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Implantable defibrillator and prevention of sudden cardiac death in patients with cardiomyopathies and channelopathies

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ABSTRACT

BACKGROUND: sudden cardiac death (SCD) due to ventricular fibrillation (VF) is a dramatic and usually unexpected event in young patients with cardiomyopathies and channelopathies including Brugada syndrome (BS). Implantable cardioverter defibrillator (ICD) is the only proven life-saving therapy in these patients, able to reduce mortality by interrupting VF. However, ICD is not free from complications and markedly affects quality of life, particularly in young and active subjects. Markers of increased arrhythmic risk are strongly needed to identify those patients who most benefit from ICD therapy. It has been reported a high incidence of BS in a Japanese population with a progressive neuromuscular disorder, the Kennedy's disease (KD). Whether the same prevalence of Brugada ECG is found in the Italian patients with KD and it represents a predictor of malignant arrhythmic outcome remains to be established.

AIMS: we aimed to: 1) found predictors of major arrhythmic events in BS, by assessing the prognostic value of clinical and electrocardiographic parameters; 2) evaluate the risk/benefit ratio of ICD in young patients (≤35 years old) with cardiomyopathies and channelopathies including BS; 3) to determine the prevalence of the Brugada ECG pattern in a large Italian cohort of patients with KD.

METHODS: we performed three different studies. First, we conducted a prospective study on 272 patients with a diagnostic (type 1) Brugada ECG either spontaneous or drug-induced. The primary end-point of the study was a combined endpoint including SCD, cardiac arrest, and appropriate ICD interventions. Second, we enrolled 96 consecutive patients with cardiomyopathies and channelopathies who were 18–35 years old at the time of ICD implantation. The study end points were cardiac mortality, appropriate ICD intervention, inappropriate ICD intervention and device-related complication. Third, we analysed 73 ECG tracings of Italian patients with KD.

RESULTS: the main results for each study were as follows: 1) during a mean follow-up of 85±44 months, 17 patients (6.3%) experienced ≥1 major arrhythmic events (annual rate 0.9%) such as appropriate ICD intervention (N=13) and SCD (N=4). History of syncope or cardiac arrest, type 1 ECG pattern and first-degree atrio-ventricular (AV) block were associated with major arrhythmic events; 2) during a mean follow-up of 72.6±53.3 months, 20 patients (20.8%) had a total of 38 appropriate ICD interventions (4%/year) and 26 patients (27.1%) experienced a total of 49 adverse ICD-related events (5.4%/year), including 23 inappropriate ICD interventions occurring in 9 patients (9.4%) and 26 device-related complications requiring surgical revision occurring in 20 patients (20.8%). One patient with end-stage hypertrophic cardiomyopathy died because of acute heart failure, and 11 patients underwent heart transplantation. Underweight status was an independent predictor of device-related complications; 3) only three patients (4%) had Brugada-like ECG changes and no patients experienced symptoms or arrhythmic events.

CONCLUSIONS: In young patients with cardiomyopathies and channelopathies ICD therapy provided life-saving protection by effectively terminating life-threatening ventricular arrhythmias. However, because ICD-related adverse events are common, the risk/benefit ratio should be carefully assessed when considering ICD implantation in young people. In addition to traditional risk predictors such as previous syncope/cardiac arrest and spontaneous type 1 pattern, we found that first-degree AV block was independently associated with a worse outcome in BS. Finally, we didn't confirm the high incidence of Brugada ECG-abnormalities previously found in a Japanese population with KD.

ABBREVIATIONS LIST

Action potential = AP

Androgen steroid hormone receptor = AR

Arrhythmogenic right ventricular cardiomyopathy = ARVC

Antitachycardia overdrive pacing = ATP

Atrio-ventricular = AV

Body mass index = BMI

Brugada syndrome = BS

Dilated cardiomyopathy = DCM

Electrophysiological study = EPS

Hypertrophic cardiomyopathy = HCM

Idiopathic ventricular fibrillation = IVF

Implantable cardioverter defibrillator = ICD

Kennedy's disease = KD

Left-ventricular noncompaction = LVNC

Long QT syndrome = LQTS

Programmed ventricular stimulation = PVS

Right ventricular outflow tract = RVOT

Short QT syndrome = SQTS

Subcutaneous ICD = S-ICD

Sudden cardiac death = SCD

Ventricular fibrillation = VF

Ventricular tachycardia = VT

BACKGROUND

Sudden cardiac death

Sudden cardiac death (SCD) is defined as an abrupt and unexpected death occurring in less than 1 hour from the first symptom onset due to a cardiovascular cause (1). It represents a major public health challenge, accounting for 20% of total mortality in the industrialised word; almost the half of patients who experience SCD are not aware of having a heart disease (2). SCD most often occurs in older adults with acquired structural heart disease, but it also rarely happens in the young, where it is more commonly due to inherited disorders. The risk of SCD increases with age and is more frequent in men. Typically, in young subjects (≤ 35 years), the causes of sudden death are mostly cardiovascular; cerebral accidents like subarachnoidal haemorrhage due to berry aneurysm rupture and respiratory causes like allergic asthma are very rare, accounting for only the 5-7% of all the sudden deaths in the young population (3). There are two principal pathophysiologic mechanisms underling SCD: a mechanical one, like in case of pulmonary embolism or cardiac acute tamponade, and an electric one responsible for more than 90% of the cases of SCD due to acute pump failure caused by ventricular fibrillation (VF) or asystole (2). Different clinical entities are responsible for SCD in the young and most of them are genetic or congenital cardiovascular diseases, while atherosclerotic coronary artery disease accounts for the vast majority of fatalities in older subject (>35 years).

Spontaneous aortic rupture in patients with bicuspid aortic valve or Marfan syndrome, congenital anomalies of the coronary arteries, cardiomyopathies like arrhythmogenic right ventricular cardiomyopathy (ARVC) or hypertrophic cardiomyopathy (HCM), valvular diseases, myocarditis, conduction system disorders like Wolff–Parkinson–White syndrome or Lenègre disease, and inherited cardiac ion

channel defects (channelopathies) like Brugada syndrome (BS), long QT syndrome, short QT syndrome and catecholaminergic polymorphic ventricular tachycardia are possible causes of SCD in the young (3). According to the main studies reporting the causes of SCD in the young, cardiomyopathies and particularly ARVC and HCM account for the majority of the cases: in young athletes, ARVC is responsible for approximately one fourth of cases in the Veneto Region of Italy and HCM for more than one third of fatal cases in the USA (4-6). A considerable proportion of young people who die suddenly have no evidence of structural heart disease and the cause of their cardiac arrest in all likelihood is related to a channelopathy.

Among different series the incidence of SCD in the young varies broadly. The difference in SCD rate reported in different studies may be explained by a variety of factors, including the age range, the proportion of men and the methodology of data collection. The rate of SCD is uncertain, but overall is low. It has been clearly demonstrated that participation in sport activity enhances the risk of SCD of approximately three times: a prospective study in the Veneto Region of Italy reported an incidence of SCD in young people between 12-35 year old of 1 per 100.000 subject per year from all causes, being 0.9 per 100.000/year in the general population and 2.3 per 100.000/year among athletes (4).

Cardiomyopathies and channelopathies

As previous reported cardiomyopathies are a leading cause of SCD among young patients and athletes. Their classification evolved in the past decades thanks to the great amount of new knowledge in genetic, molecular biology and pathophysiology and to the discovery of new clinical entities. The World Health Organization wrote the first classification of cardiomyopathies in 1980, based upon the principle to distinguish heart muscle diseases in two main groups according to the cause (known

or unknown). Cardiomyopathies were considered as “heart muscle diseases of unknown cause” and were distinguished according to the predominant structural and hemodynamic phenotype in three categories: dilated, hypertrophic and restrictive cardiomyopathy. Besides primitive cardiomyopathies, they classified specific heart muscle diseases as “heart muscle diseases of known cause or associated with disorders of other systems”. Cardiac disorders due to systemic or pulmonary hypertension, coronary artery, valvular or pericardial disease or congenital cardiac anomalies were excluded from both the categories (7). In 1995 the discovery of new clinical entities brought to a revision of the first classification. Cardiomyopathies were redefined as “diseases of the myocardium associated with cardiac dysfunction” and specific heart muscle diseases were named specific cardiomyopathies and defined as “heart muscle diseases associated with specific cardiac or systemic disorder”. ARVC, left ventricular noncompaction (LVNC) and idiopathic restrictive cardiomyopathy were added to the new classification in the cardiomyopathy group. In the specific cardiomyopathies group were included myocarditis, called “inflammatory cardiomyopathy”, and ischemic, valvular and hypertensive disorders (8).

The 1995 Task Force report had the merit of recognising new clinical entities and including myocarditis as inflammatory cardiomyopathies, but two major concerns arise from this new classification. First, the concept of specific cardiomyopathies was extended too much to include ischemic, valvular and hypertensive disease and this brought ambiguities about the original meaning of cardiomyopathies. Second, the idea of dysfunction was limited to the mechanical abnormalities and excluded electrical disturbances (9).

The rapid evolution of genetic and molecular biology in cardiology brought to the discovery of gene mutations as the basis of most of the known cardiomyopathies. On the other hands, patients suffering rhythm disturbances and SCD presenting without any manifest structural abnormalities were recognised to be affected by

"channelopathies", defined as inherited cardiac electric disorder due to mutation in ion channels. Although no macroscopic alterations are detectable in channelopathies, the structure of myocytes is altered at the molecular level because of the presence of mutated proteins. This brought to a necessary revision of the 1995 WHO classification (9).

The American Heart Association published a new definition and classification of cardiomyopathies in 2006. Cardiomyopathies were defined as *"a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure–related disability.*

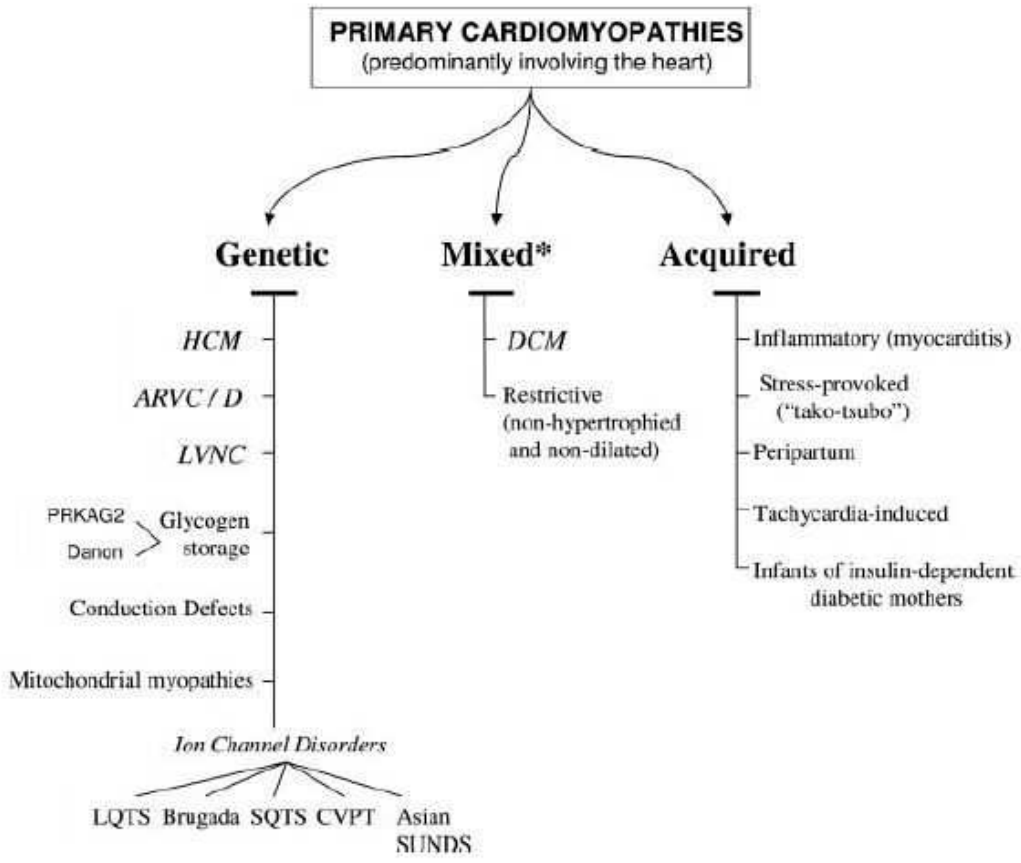

Figure 1. Primary cardiomyopathies *(Adapted from Maron et al. Circulation 2006 113: 1807-1816)*.

They were divided into 2 groups based on predominant organ involvement. *Primary* cardiomyopathies are those predominantly confined to heart muscle; *secondary* cardiomyopathies show pathological myocardial involvement as part of a large number and variety of generalized systemic multiorgan disorders. Among primary cardiomyopathies, they recognised 3 subgroups based on the different aetiology: genetic, mixed (genetic and non genetic) and acquired (Figure 1). Channelopathies or ion channel disorders were included in the genetic group. Cardiac disease secondary to other cardiovascular abnormalities like valvular heart disease, systemic hypertension, coronary artery disease and congenital heart defect were not included in this scheme.

The AHA classification introduced two important innovations; the first was that the classification was no more based on phenotypic expression but on the genetic aetiology. The second one was the introduction of the channelopathies among primary genetic cardiomyopathies, introducing the concept of a primary electrical dysfunction of the heart muscle (10).

Dilated Cardiomyopathy

Definition and epidemiology

According to the AHA classification, dilated cardiomyopathy (DCM) is included in the groups of primary cardiomyopathies with mixed origin and is characterised by the presence of left ventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions (hypertension, valvular heart disease) or coronary artery disease that justify the global systolic impairment (10, 11).

It has an overall prevalence of 40 cases per 100000 individuals with an annual incidence of 7 cases per 100000 individuals and it is more common in men. It

represents a leading cause of heart failure and SCD and it is the most common indication for heart transplantation (12, 13).

Aetiology

A pathogenic mutation account for at least 20% of cases of DCM and most commonly is inherited as an autosomal dominant trait. The principal mutated genes encode for sarcomeric proteins like cardiac troponin T, myosin heavy chain and myosin-binding protein C, and for cytoskeletal proteins like lamin A/C or titin. A particular X-linked type of DCM is caused by mutations in the dystrophin gene (10-14). Many acquired conditions are responsible for DCM, including infective agents, autoimmune and systemic diseases, toxins (alcohol, cocaine, methamphetamines), cytotoxis drugs (anthracyclines) and metabolic disorders. Among infective agents, virus like coxsackievirus B, parvovirus B19, human herpes virus 6 and adenovirus are often involved in the pathogenesis of DCM (10, 11, 13).

Clinical presentation and diagnosis

DCM manifest with the typical heart failure symptoms in almost 80% of patients and the presentation can be acute and fulminant or chronic. The major causes of cardiovascular death are worsening heart failure or SCD secondary to ventricular arrhythmia, fatal bradi-arrhythmias or electromechanical dissociation; SCD occurs in up to 12% of patients with this disorder and accounts for 25–30% of all deaths (13).
Diagnosis relies on patient history, and clinical, echocardiographic, or cardiac MRI features of dilated cardiomyopathy or heart failure. The definite diagnosis is made by the presence of a reduced ejection fraction of the left ventricle (less than 45%) and left ventricular enlargement, excluding any myocardial diseases that could be responsible for the clinical scenario (12, 13).

Risk stratification and treatment

First line therapy is mainly directed at treatment of heart-failure symptoms and at prevention of SCD.

Drugs used in these patients are those that have been shown in large-scale clinical trials to improve survival and reduce hospital admissions in heart failure, like angiotensin converting enzyme inhibitors, β blockers and mineralocorticoid antagonists (11, 13). Optimal medical therapy is recommended in order to reduce the risk of progressive heart failure but also to prevent SCD (11).

While no doubt exists about the benefit of implantable cardioverter defibrillator (ICD) implantation for the prevention of SCD in patients with previous history of cardiac arrest or haemodynamically not tolerated sustained VT (11), the evidence of the benefit of ICD in primary prevention is less clear. Many non-invasive variables have been proposed as predictor of SCD, but the only parameter actually used for risk stratification is the degree of left ventricular dysfunction (11). The first randomised studies evaluating the benefit of ICD therapy in patients with non-ischaemic cardiomyopathy with marked reduced ejection fraction, like the SCD-HeFT trial or the COMPANION trial, demonstrated a reduction of all-cause death in the ICD arm (15, 16). The current Guidelines of the European Society of Cardiology, both for heart failure (2016) and for management of patients with ventricular arrhythmias and the prevention of SCD (2015), recommend an ICD in patients with DCM “to reduce the risk of sudden death and all-cause mortality in patients with symptomatic heart failure (NYHA class II–III), and a left ventricular ejection fraction ≤35% despite ≥3 months of optimal medical therapy, provided they are expected to survive substantially longer than 1 year with good functional status (class I, level B)” (11, 17). The Danish study is a randomised trial published in 2016 comparing conventional medical treatment with conventional medical treatment plus ICD in patients with heart failure and DCM. The main clinical result was the no reduction in the primary endpoint of all-cause death for patients randomised to ICD therapy; this was despite a significant reduction in sudden cardiac death in the ICD group (18).

Taken together all this data highlight the limited value of ejection fraction of the left ventricle in risk stratification and underline the need of new and stronger parameters for prognostic evaluation in DCM.

In patients with DCM and recurrent VT refractory to medical therapy, catheter ablation is recommended to reduce the incidence of arrhythmic episodes and to reduce the number of appropriate ICD intervention (11).

Heart transplantation and implantation of long-term mechanical circulatory supports the final therapy for patients with refractory heart failure (NYHA Class IV) (13).

Hypertrophic cardiomyopathy

Definition and epidemiology

HCM in a genetic primary cardiomyopathy defined by the presence of increased left ventricular wall thickness that is not solely explained by abnormal loading conditions (12, 20). It is a common inherited heart disease, with a prevalence of at least one in 500 in the general population and represents a major cause of SCD in the young, of heart failure and of atrial fibrillation (19, 21, 22).

Genetics

In more than a half of the patients with HCM, the disease is an autosomal dominant trait caused by mutations in cardiac contractile myofilament protein components of the sarcomere or the adjacent Z-disc (19, 20). Mutations in two genes, β-myosin heavy chain and myosin-binding protein C, account for the majority of cases (23). Systemic disorders including inherited metabolic and neuromuscular diseases, chromosome abnormalities and genetic syndromes are responsible for the other cases of HCM not caused by sarcomeric gene mutations (19).

The variability of the phenotypic expression of HCM suggests that the single gene mutation is not the only determinant of the clinical phenotype.

Clinical presentation and diagnosis

Clinical course of HCM could be very variable, ranging from people that achieve normal life expectancy with little or no disability to people who experience high morbidity and mortality; the three principal adverse pathways that might occur in affected patients are atrial fibrillation, heart failure and SCD due to VT/VF (19, 20).

Mortality rate in HCM is low, about 1% per year, heart failure and thromboembolism being the main causes of death. Nevertheless, HCM is the most common cause of SCD in young people and athletes and in most cases SCD occurs in asymptomatic subjects without warning sign (19, 20, 22).

Heart failure with preserved ejection fraction is normally due to diastolic dysfunction and small LV size; atrial fibrillation and mitral regurgitation could exacerbate symptoms. Evolution of the disease might include decline of the systolic function of the left ventricle with end stage heart failure (NYHA III-IV). Structural heart changes with progressive cardiac remodelling and myocardial fibrosis are usually subclinical in the first stages of the disease and patients could remain asymptomatic for long time (19, 20). Clinical factors correlated with the evolution of heart failure are a LV outflow tract pressure gradient ≥30 mm Hg at rest and the diastolic dysfunction (24, 25).

Atrial fibrillations' prevalence is 4-fold greater than in the normal population and is associated with worse heart failure symptoms and stroke (26).

The diagnosis relies on the identification of increased LV wall thickness by any imaging modality. According to the 2014 European Guidelines on diagnosis and management of hypertrophic cardiomyopathy, "in an adult, HCM is defined by a wall thickness ≥15 mm in one or more LV myocardial segments—as measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging or computed tomography) that is not explained solely by loading conditions" (20).

Risk stratification and treatment

Multiple risk factors have been used to assess the arrhythmic risk and guide ICD therapy in HCM patients in primary prevention, like the presence of non-sustained VT, maximal LV wall thickness ≥30mm, family history of SCD, unexplained syncope, and abnormal blood pressure response to exercise. Other clinical characteristics like myocardial fibrosis (determined by contrast enhanced CMR), LV apical aneurysms and the inheritance of multiple sarcomere protein gene mutations have been correlated with an unfavourable arrhythmic outcome (19, 20). The 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy proposed to use the "HCM Risk-SCD model" to predict the 5-year risk of SCD and to guide ICD therapy (19, 27). This risk prediction model uses predictor variables that have been associated with an increased risk of SCD in at least one published multivariable analysis and includes: age, family history of SCD, unexplained syncope, left ventricular outflow gradient, maximum left ventricular wall thickness, left atrial diameter, NSVT. ICD implantation for primary prevention is recommended in patients with an estimated 5-year risk of SCD of ≥more than 6% (high risk group) and a life expectancy of >1 year. ICD implantation is not recommended in patients with an estimated 5-year risk of SCD of <4% (low-risk group) and no other clinical features that are of proven prognostic importance. In patients with an intermediate risk (5–year risk 4-<6%) ICD may be considered (19). Finally, ICD implantation is recommended in patients who experienced a cardiac arrest due to VT/VF, or who have spontaneous sustained VT causing syncope or haemodynamic compromise, and have a life expectancy of >1 year (19).

ICD is the only treatment option with proven effectiveness in preventing SCD, while antiarrhythmic drug therapy should be used only for symptom relief (19, 28).

In the study from Maron *et al.* conducted in 500 high-risk patients with HCM, the incidence rate of appropriate ICD intervention was 10.6%/year in secondary prevention and 3.6%/year in primary prevention; 20% of the total population

experienced appropriate ICD intervention on VT/VT, while 27% experienced ICD related complications including also inappropriate ICD interventions (29).

A meta-analysis from published studies on outcome and complications after ICD therapy in patients with HCM was published in 2012; the annualized rate of appropriate ICD interventions was 3.3%, 83% of the population receiving an ICD for primary prevention of SCD. The annualized inappropriate ICD intervention rate was 4.8% and the annualized ICD-related complication rate was 3.4% (30).

Finally, another study from Maron *et al.* conducted in 224 children and adolescents with HCM judged at high risk, reported an ICD intervention rate of 4.5% per year overall, 14% per year for secondary prevention, and 3.1% per year for primary prevention. Over a mean follow-up of 4.3±3.3 years, 91 patients (40%) experienced at least 1 device-related complication (9.5% per year), particularly inappropriate shocks and lead malfunction (31).

Arrhythmogenic right ventricular cardiomyopathy

Definition and epidemiology

ARVC is an inherited heart muscle disease that predominantly affects the right ventricle, classified ad a genetic primary cardiomyopathy. It is characterized pathologically by right ventricular myocardial atrophy with fibro-fatty replacement, which acts as a substrate of ventricular electric instability with VT or VF that may lead to SCD mostly in young people and athletes. Later in the disease course, progression of right ventricular muscle disease and left ventricular involvement may result in heart failure (32-35).

It is a rare disease, with a prevalence of 1:5.000 in the general population. The disease affects men more frequently than women, with an approximate ratio of 3:1 and becomes clinically overt most often in the third or fourth decade of age (35).

Genetics

A familial background has been demonstrated in 50% of ARVC cases. The disease is usually inherited as an autosomal dominant trait with incomplete penetrance and variable expression. It is a desmosomal disease resulting from defective cell adhesion proteins (36). The first disease-causing gene, the JUP gene, was identified by McKoy *et al.* in patients with Naxos disease, a particular type of ARVC with a autosomal recessive transmission (37). The gene encodes the desmosomal protein plakoglobin, a major constituent of cell adhesion junction. Other desmosomal genes associated with ARVC with an autosomal dominant inheritance are desmoplakin, plakophilin-2 desmoglein-2 and desmocollin-2. Autosomal dominant ARVC has been linked to other genes unrelated to cell adhesion complex, such as the gene encoding for cardiac ryanodine receptor and the transforming growth factor-β-3 gene. The rare ARVC-5 variant, which is characterized by a defect of TMeM43 gene, encoding for a transmembrane protein, is associated with a fully penetrant and lethal presentation (38).

Clinical presentation and diagnosis

The clinical phenotype of ARVC varies considerably ranging from asymptomatic family members with concealed right ventricular structural abnormalities and no arrhythmias to patients experiencing arrhythmic cardiac arrest or undergoing cardiac transplantation due to right or biventricular heart failure. The natural history of ARVC is predominantly related to ventricular electrical instability, which may lead to arrhythmic SCD. In advanced disease, progression of right ventricular muscle disease and left ventricular involvement may result in right or biventricular heart failure. The following phases in the disease natural history can be considered: 1) “concealed” characterized by no or subtle right ventricular structural changes, with or without minor ventricular arrhythmias, during which SCD may occasionally be the first manifestation of the disease, mostly in young people during competitive sports

or intense physical exercise; 2) “Overt electrical disorder” in which symptomatic right ventricular arrhythmias possibly leading to sudden cardiac arrest are associated with overt right ventricular functional and structural abnormalities; 3) “right ventricular failure” caused by the progression and extension of muscle disease that provoke global right ventricular dysfunction with relatively preserved left ventricular function. 4) “Biventricular pump failure” caused by pronounced left ventricular involvement, mimicking biventricular dilated cardiomyopathy (32-35).

There is no single test sufficiently specific for diagnosing ARVC, and thus multiple criteria are needed. The diagnosis relies on a scoring system based on structural, histological, electrocardiographic, arrhythmic, and familial features of the disease. The original 1994 International Task Force Criteria have been proposed on the basis of the first experience with ARVC patients, who were mostly symptomatic index cases with an overt disease and/or sudden death victims (39). Because of the lack of sensitivity for identification of minor phenotypes and the absence of quantitative cut-off values, these criteria were revised in 2010 to improve diagnostic sensitivity while maintaining diagnostic specificity (40).

Risk stratification and treatment

The role of ICD therapy in patients with overt disease and high risk of SCD (survivors from a cardiac arrest and patients with sustained VT) is well established. The first study to demonstrate the survival benefit of ICD in ARVC was the Darvin I study (41). Patients who received ICD because of cardiac arrest or VT with hemodynamic compromise showed a high incidence of VF during follow-up (10% per year of follow-up). Clinical predictors of SCD in the subgroup of patients with ARVC who did not experience cardiac arrest or VT were investigated by the multicentre observational study by Corrado *et al.* (“Darvin II” study); they found that syncope was the only independent predictor of appropriate ICD interventions (42). Beside syncope, different studies identified other predictors of arrhythmic events during

follow-up in patients with ARVC e no history of cardiac arrest. The most important were the presence of non-sustained VT, dysfunction of the right or left ventricle, inducibility at programmed ventricular stimulation (PVS) and the demonstration of bipolar RV electroanatomic scar area during endocardial voltage mapping (43, 44).

The meta-analysis by Schinkel on the efficacy and safety of ICD therapy in ARVC patients both for primary or secondary prevention demonstrated a very low annual cardiac mortality rate (0.9%) and an annual rate of appropriate ICD intervention of 9.5%. On the other hands, rates of complications, mostly due to lead failure or inappropriate ICD interventions, were respectively of 4.4%/year and 3.7%/year (45).

During the 2015 International Task Force on the treatment of ARVC (46) indications for ICD implantation were formulated (Figure 2).

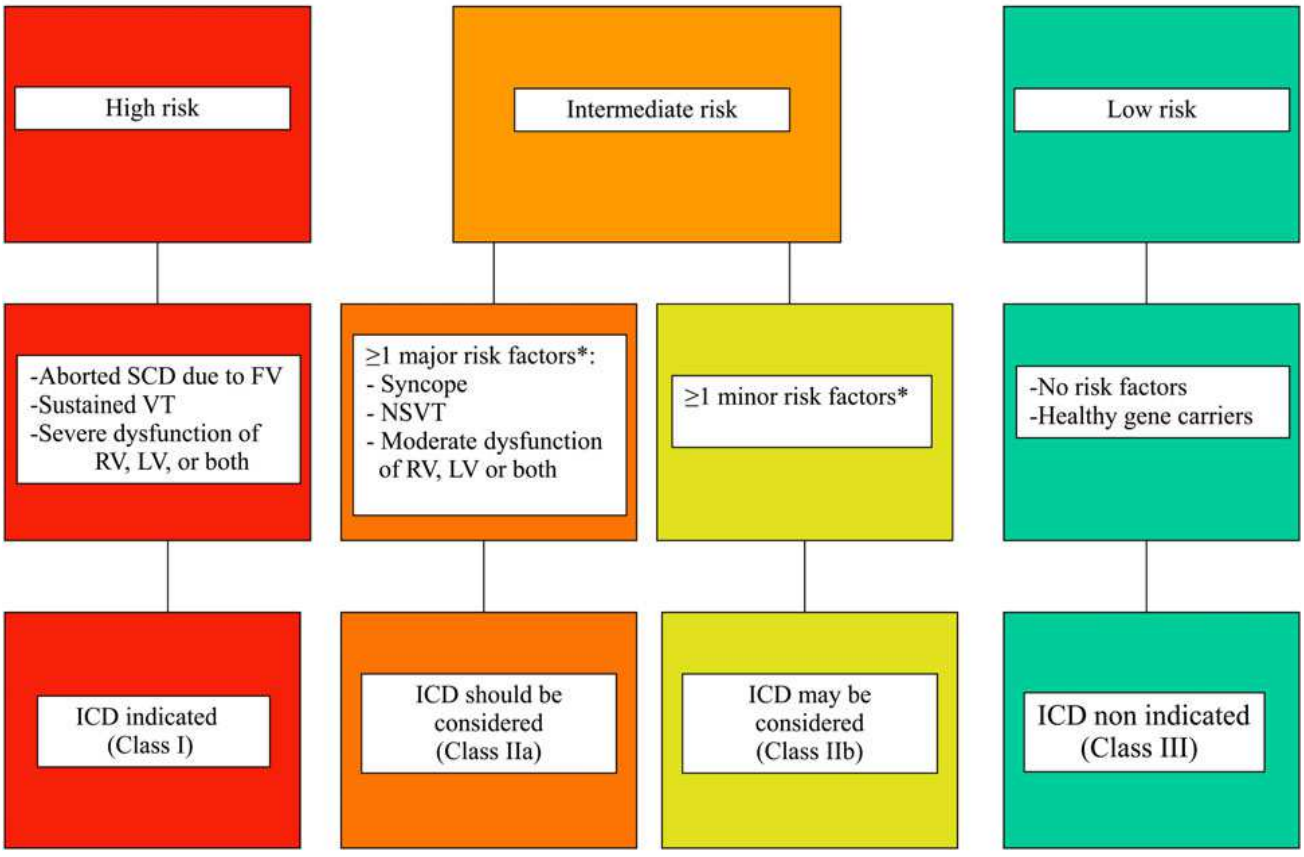

Figure 2. Flow chart of risk stratification and indications to ICD implantation in ARVC *(Adapted from Corrado et al. Circulation 2015;132:441-53).*

Major risk factors included syncope, non-sustained VT or moderate ventricular dysfunction. Minor risks factors were male gender, compound and digenic heterozygosity of desmosomal-gene mutations, young age at the time of diagnosis, proband status, inducibility at PVS; amount of electroanatomic scar and electroanatomic scar-related fractionated electrograms; extent of T-wave inversion across precordial and inferior leads; low QRS amplitude and QRS fragmentation.

Antiarrhythmic drug therapy and catheter ablation are useful to control symptoms and reduce ICD discharge, but cannot replace ICD in the prevention of SCD (46).

Finally, in patients with right or left ventricular dysfunction, standard heart failure treatment is recommended (46).

Left-ventricular noncompaction

Definition and epidemiology

LVNC is a rare genetic primary cardiomyopathy characterised by abnormal trabeculations in the left ventricle, most frequently at the apex, creating two distinct layers: compacted and non-compacted (47, 48). LVNC may be an isolated finding or may be associated with other congenital heart anomalies such as complex cyanotic congenital heart disease (49).

Genetics

Genetic inheritance is found in at least 30-40% of the patients and is most often autosomal dominant (49). Usually sarcomeric or cytoskeletal proteins are involved.

Clinical presentation and diagnosis

Clinical presentation of LVNC is highly variable; some patients could be asymptomatic but others may present with end-stage heart failure, lethal arrhythmias, SCD, or thromboembolic events.

Risk stratification and treatment

Giving the very low prevalence of the disease risk stratification, treatment and indications to ICD implantation should follow the same criteria for DCM (11).

Long QT syndrome

Definition and epidemiology

Congenital LQTS is an inherited ion channel disease characterised by a prolongation of the QT interval at basal ECG and the occurrence of syncope or cardiac arrest due to ventricular arrhythmias, mainly precipitated by emotional or physical stress (50, 51). The prevalence of the disease has been estimated to be 1:2000 (52).

Genetics

Tree main types of LQTS have been identified based in the disease-causing gene, accounting for 90% of all genotype-positive cases. LQTS-1 is caused by a loss of function mutation of the potassium channel *KCNQ1*. Heterozygous *KCNQ1* mutations cause the dominant Romano-Ward LQT-1 syndrome and account for the majority of disease-causing variants. Homozygous mutations in *KCNQ1*, or compound heterozygous mutations, cause the recessive Jervell and Lange-Nielsen variant, characterized by deafness (51). LQTS-2 is associated with a loss of function mutation of the potassium channel *KCNH2*. The third most common gene is the *SCN5A* gene, encoding for the α-subunit of the cardiac sodium channel: gain of function mutations of this protein cause the LQTS-3 (51).

Clinical presentation and diagnosis

The two fundamental clinical manifestations of the syndrome are the presence of ECG abnormalities at the basal ECG (QT prolongation and T wave abnormalities) and

of typical symptoms like syncope, cardiac arrest or SCD due to VT. The typical ventricular arrhythmia is the “Torsades-de-Pointes”, a rapid polymorphic VT that can be self-terminating causing syncope or can degenerate in VF with cardiac arrest or SCD (53). According to the genotype, ventricular arrhythmias are triggered but different factors. Stress or physical activity induce VT in LQTS-1, Conversely, most of the events of LQT2 patients occur during emotional stress such as auditory stimuli (sudden noises especially at rest) while for LQT3 patients they occur during sleep or at rest (53).

Diagnosis relies on the measurement of a prolonged correct-QT interval (QTc) on surface ECG; secondary causes of QT prolongation must be excluded (drugs, electrolyte imbalance, acquired cardiac conditions). According to the 2015 ESC Guidelines for management of patients with ventricular arrhythmias and the prevention of SCD, the diagnosis is made when there is a QTc ≥ 480 ms at the basal ECG or a LQTS risk score ≥ 3 in the absence of a secondary cause for QT prolongation; alternatively, the diagnosis is established when there is an unequivocally pathogenic mutation in one of the LQTS genes (11). The scoring system predicts the probability of the diagnosis and takes into account the age of the patient, medical and family history, symptoms, ECG abnormalities and QTc duration (54, 55).

Risk stratification and treatment

Beta-blockers are the first line therapy for patients with LQTS. In high-risk patients symptomatic on beta-blocker therapy or who have contraindications/intolerance to beta-blockers, left cardiac sympathetic denervation is recommended; it could be also used in case of recurrent ICD interventions despite pharmacological therapy (11, 56). Lifestyle changes are also recommended, like avoidance of QT- prolonging drugs or of genotype-specific triggers for arrhythmias, correction of electrolyte abnormalities (11).

Cardiac arrest survivors have a high rate of recurrences of malignant arrhythmias even when receiving beta-blocker therapy, so ICD implantation is mandatory (11). Arrhythmic risk stratification in patients with LQTS and no previous cardiac arrest is based on electrocardiographic, clinical and genetic characteristics. According to the 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, ICD should be considered in patients with syncope during beta-blocker therapy; in asymptomatic carriers, ICD may be considered in case of malignant gene mutations when QTc is > 500 ms (11). Of note, LQTS is the only channelopathy where the genetic characterisation of the patients has an important role in arrhythmic risk stratification.

A multicentre registry prospectively evaluated 223 patients with LQTS who underwent ICD implantation. During a follow-up of more than 4 years, at least 1 appropriate shock was received by 28% of patients, and adverse events including inappropriate ICD interventions or device related complications such as lead failure occurred in 25% (57).

Short QT syndrome

Definition and epidemiology

SQTS is a rare inherited ion channel disease characterised by a shortening of the QT interval at basal ECG, SCD and the occurrence of atrial fibrillation; it was first described in 2000 (58).

Genetics

Gain-of-function mutations in genes encoding for potassium channels (KCNH2, KCNQ1, KCNJ2) and loss-of-function mutations in gene encoding L-type calcium channel subunits (CACNA1C and CACNB2b) have been identified (59).

Clinical presentation and diagnosis

Patients typically present with a short QT interval at basal ECG, history of atrial fibrillation at young age and ventricular arrhythmia (59).

There is still no clear consensus for the definition of the lower limit of the QT interval; the ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death suggest 340 ms as cut of limit for the diagnosis of SQTS. In case of a confirmed gene mutation, a family history of SQTS or SCD and previous cardiac arrest a cut off value of 360 ms could be used (11).

Risk stratification and treatment

ICD implantation is recommended in patients with previous cardiac arrest or sustained VT. Given the very low prevalence of the disease clear data on risk stratification do not exist, the decision whether to implant or not an ICD should be made case by case.

Quinidine is the only drug that can prolong QT interval and should be used in patients who have contraindication to the ICD or refuse it (11).

Idiopathic ventricular fibrillation

IVF is characterized by spontaneous VF in the absence of any identifiable structural or functional cardiac disease. The discovery of channelopathies has reduced over time the percentage of cardiac arrest without an underlying cardiac disease, nevertheless IVF still accounts for a small portion of patients resuscitated from out-of-hospital cardiac arrest (60).

ICD implantation is recommended in these patients. A meta-analysis of the outcome of patients with IVF found that 31% of the population experienced a recurrence of VT during follow-up (60).

Focus on Brugada Syndrome

Definition, classification and epidemiology

Brugada Syndrome (BS) is a genetic disease with an autosomal dominant inheritance pattern and incomplete penetrance; it is characterised by the presence of typical electrocardiographic abnormalities, ventricular arrhythmias and increased risk of sudden cardiac death (SCD) in the absence of a structural cardiac disease (61-63). The first report of the disease was published in 1992 by Josep and Pedro Brugada: they described eight patients with recurrent episodes of unexplained aborted sudden death presenting with "right bundle branch block, persistent ST segment elevation in precordial leads not explained by electrolyte disturbances, ischemia or structural heart disease" (61). Typical ECG abnormalities both of repolarisation and of depolarisation are the hallmark of this syndrome; three electrocardiographic repolarization patterns in the right precordial leads are described (Figure 3). Type 1 (*coved-type*) is characterized by a prominent coved ST-segment elevation displaying J wave amplitude or ST-segment elevation ≥ 2 mm (0.2 mV) followed by a negative T wave with little or no isoelectric separation in ≥ 1 right precordial lead (V1-V3) (Figure 3). Type 2 (*saddleback-type*) has a high take-off ST-segment elevation, with the J wave amplitude ≥ 2 mm, giving rise to a gradually descending ST-segment elevation (remaining ≥ 1 mm above the baseline), followed by a positive or biphasic T-wave. Type 3 has either a saddleback or coved appearance with an ST-segment elevation of <1 mm. These 3 patterns may be observed spontaneously at different

time in serial ECG tracings from the same patient or after the introduction of specific drugs. These ECG patterns are usually detected by positioning the right precordial leads in the fourth intercostal space; the placement of the right precordial leads in a superior position (in the second or third intercostal space) can increase the sensitivity of the ECG for detecting the Brugada phenotype in some cases (64, 65).

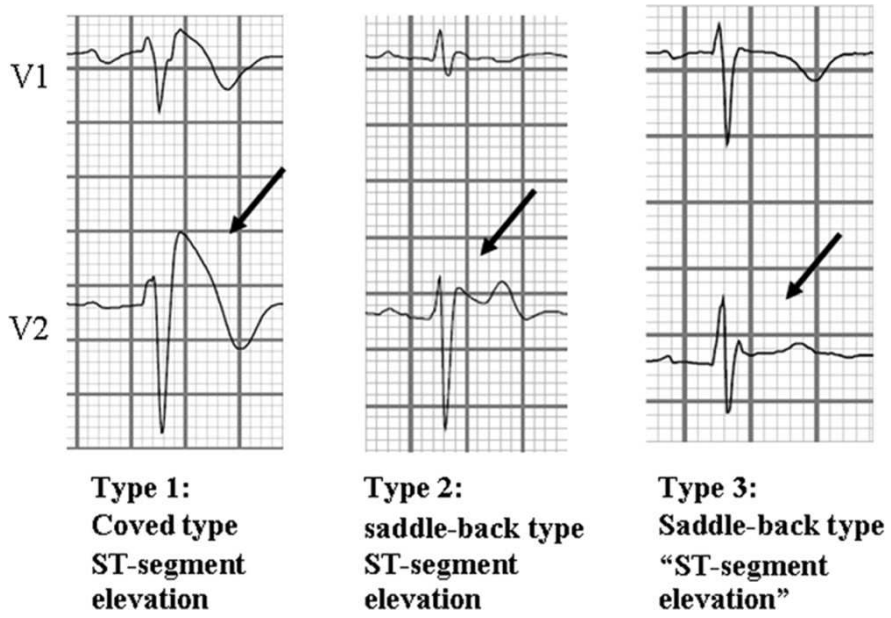

Figure 3. Three electrocardiographic repolarization patterns in the right precordial leads in Brugada syndrome *(Adapted from Mizusawa et al. Circ Arrhtthm Electrophysiol 2012; 5(3):606-16).*

ECG characteristics include also depolarisation abnormalities like conduction disturbances, pronounced S waves in the inferior leads creating the typical S1S2S3 pattern and atrio-ventricular (AV) first-degree block. Typical clinical manifestations of the syndrome include unexplained cardiac arrest, documented ventricular tachycardia, syncope and nocturnal agonal respiration; atrial fibrillation has higher prevalence in these patients.

BS is included in the "*Contemporary definitions and Classification of Cardiomyopathies"* published in 2006 under the auspices of the American Heart Association (10). During the decades before the publication of this consensus panel, the identification of new pathological entities and the important advantages in the

pathophysiology, diagnosis and therapy in this field brought to the need of a more rigorous definition and classification of cardiomyopathies. Particularly, the new molecular genetics knowledge in cardiology allowed the discovery of the ion channelopathies, like BS; they are defined as cardiomyopathies predisposing to ventricular tachyarrhythmia and SCD in the absence of functional and structural myocardial abnormalities. Channelopathies are primary electrical disease, caused by mutations in ion channel proteins leading to dysfunctional sodium, potassium, calcium, and other ion channels; they are classified like primary genetic cardiomyopathies (Figure 1).

BS is more frequent and with a worse prognosis in male than in female (M:F = 10:1) (66); it affects normally young men during adulthood, with a mean age of sudden death of 41±5 years (62). It accounts for at least 4% of all sudden deaths and at least 20% of sudden deaths in patients with structurally normal hearts. The true prevalence of the disease is difficult to estimate, because of the dynamic presence of the ECG pattern in the same subject in different moment and because of the different geographic distribution, being the syndrome endemic in Asian countries. The global prevalence of Brugada syndrome varies from 5 to 20 cases in every 10,000 inhabitants worldwide. In a Japanese study of 2001, a Brugada diagnostic ECG (type 1) was observed in 12/10000 inhabitants; type 2 and 3 ECGs (not diagnostic), were much more prevalent, appearing in 58/10000 inhabitants; the prevalence of the BS among the general population in Europe and the United States is thought to be much lower (62, 67).

Genetic basis

In 1998, Chen *et al.* found the first mutation linked to BS in the *SCN5A* gene, which encodes for the α-subunit of the sodium channel protein $Na_v1.5$ (68).

since then, more than 300 *SCN5A* gene mutations have been identified in BS patients.

Table 1. Gene defects associated with Brugada Syndrome *(modified from Antzelevitch et al. Europace 2017; 19(4): 665-94).*

Gene/protein	Ion Channel	Percent of probands
SCN5A, $Na_v1.5$	**↓ INa**	11-28%
GPD1L	**↓ INa**	Rare
CACNA1C, Cav1.2	**↓ ICa**	6.6%
***CACNB2b,* Cav*β*2b**	**↓ ICa**	4.8%
SCN1B, Na_Vß1	**↓ INa**	1.1%
KCNE3, MiRP2	**↑ Ito**	Rare
SCN3B, Navß3	**↓ INa**	Rare
KCNJ8, Kir6.1	**↑ IK-ATP**	2%
CACNA2D1, Cava2d1	**↓ ICa**	1.8%
KCND3, Kv4.3	**↑ Ito**	Rare
RANGRF, MOG1	**↓ INa**	Rare
SLMAP	**↓ INa**	Rare
ABCC9, SUR2A	**↑ IK-ATP**	Rare
SCN2B, Navß2	**↓ INa**	Rare
PKP2, Plakophillin-2	**↓ INa**	Rare
FGF12, FHAF1	**↓ INa**	Rare
SCN10A, Nav1.8	**↓ INa**	5-16.7%
HEY2	**↑ INa**	Rare

SCN5A mutations cause *loss-of-function* of the sodium channel $Na_v1.5$ resulting in a reduction in I_{Na} current with different mechanisms: decreased expression of the sodium channel protein in sarcolemma, expression of non-functional channels, or altered gating properties (delayed activation, earlier inactivation, faster inactivation, enhanced slow inactivation, and delayed recovery from inactivation).

SCN5A loss-of-function mutations may cause not only BS but also may lead to other diseases, like progressive cardiac conduction disease, Lenegre disease and sick sinus syndrome; *SCN5A gain-of-function* mutations contribute to the development of atrial fibrillation and long-QT-syndrome (65, 69, 70).

SCN5A mutations are the most common type in BS, accounting for 11–28% of BS probands, but to date mutations in 18 different genes have been associated to BS, most of all encoding for ionic channels protein (70) (Table 1).

Mutations in genes encoding the proteins of the calcium channels *CACNA1C* (Cav1.2), *CACNB2b* (Cav*β*2b) and *CACNA2D1* (Cav*α*2*δ*) have been reported in up to 13% of probands; these mutations cause a loss of function of basal *L*-type calcium current (65, 71-73). Patients with mutations into *CACNA1C* and *CACNB2b* generally present with shorter-than-normal QT intervals (73). Other genes have been associated more rarely to BS, like sodium channel β-subunit genes (*SCN1B*, *SCN3B*), glycereol-3 phosphate dehydrogenase 1-like enzyme (*GPD1L*) and *MOG1*, and genes encoding for potassium channels (*KCNE3, KCND3*) (74-77). Mutations in *SCN1B*, *SCN3B*, *GPD1L*, or *MOG1* genes led to loss of function of the sodium current; mutations in the potassium channel proteins bring to a gain of function of the transient outward potassium currents (65,70). One of the most recent gene associated with BS is the SCN10A, a neuronal sodium channel; mutations in this gene are responsible for a loss of function in sodium (I_{Na}) and calcium (I_{Ca}) channel currents, as well as to a gain of function in transient outward potassium current (I_{to}) or ATP-sensitive potassium current ($I_{K\text{-}ATP}$) (78, 79). Despite the great amount of data on the genetic background of BS, studies proving the causality between a gene

mutation and BS are still lacking. In most cases gene mutation alone cannot completely explain the phenotype and may act mostly as modifiers rather than cause. Data from genetic studies have brought to the concept that BS phenotype is the results of inheritance of multiple BS susceptibility variants acting in concert; moreover, the complexity of the genetic predisposition can be modulated by non-genetic factors, like hormonal and other environmental factors (70, 80).

Physiopathology and arrhythmogenesis

Over the paste decades, the pathophysiological mechanism underling the ECG features and the arrhythmogenesis in BS has been investigated but it still remains a matter of debate. Two leading hypotheses have been advanced, the repolarization hypothesis and the depolarization hypothesis.

The repolarization hypothesis

To understand the cellular basis of electrocardiographic J wave and of arrhythmogenesis in BS according to the repolarization hypothesis, it is necessary to know the basic principles of cardiac electrophysiology. The cardiomyocyte cell membrane is a hydrophobic milieu made of lipids, so ions, that are hydrophilic, cannot directly cross it and need specialized proteins, the ion channels, to penetrate the cell membrane; most cardiac ion channel are both time and voltage dependent. The action potential (AP) begins when the transmembrane potential of the cardiomyocytes become more positive; in response to this signal the sodium voltage-dependent channels Nav1.5 move from the “closed” configuration to the “activated” configuration, generating the inward sodium current (I_{Na}) responsible for the depolarization “phase 0” of the AP (Figure 4). The rapid cell depolarization activates potassium and calcium channels and brings the sodium channels to the

"inactivated" form. During the "phase 1" of the AP called early repolarization an outward potassium current (I_{to}) is responsible for a rapid and short deflection (notch) of the AP. The rapid cell depolarization activates potassium and calcium channels and brings the sodium channels to the "inactivated" form. During the "phase 1" of the AP called early repolarization an outward potassium current (I_{to}) is responsible for a rapid and short deflection (notch) of the AP.

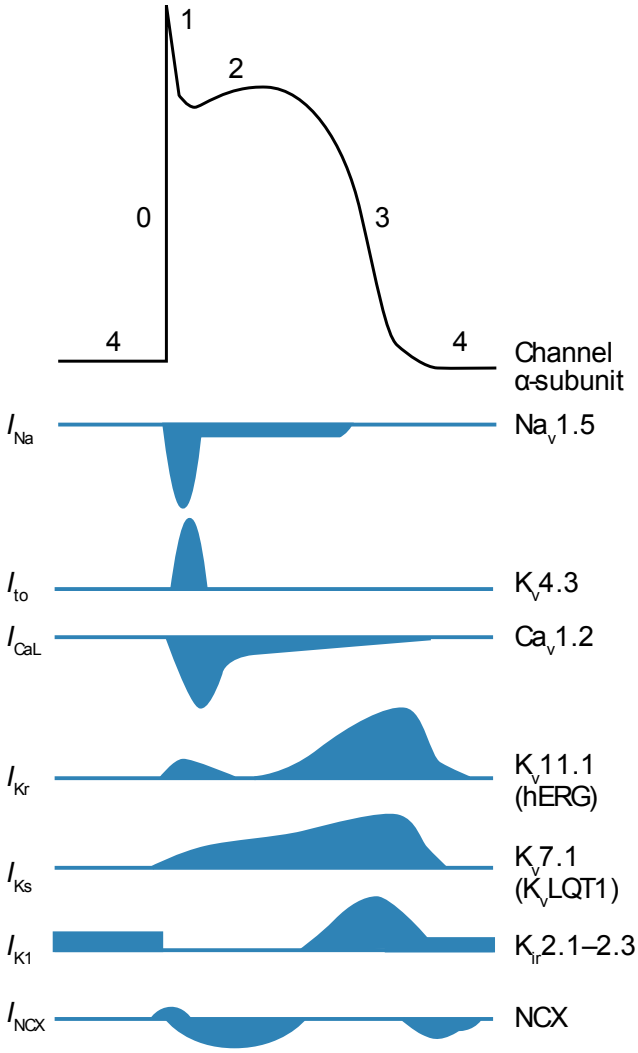

Figure 4. The cardiac action potential and the major contributing cardiac ion channel currents *(Adapted from Liu et al. Nat Rev Cardiol 2014; 11(10): 607-15)*.

The activity of the L-type calcium channels is responsible for the "phase 2" or plateau phase of the AP, where the outward repolarising potassium currents (I_{Ks} and I_{Kr}) are balanced by the inward depolarising calcium current. Finally, during the

"phase 3" or repolarization phase the calcium channels are gradually inactivated and the outflow of potassium exceed the inflow of calcium, brining the membrane cell to the resting potential.

The notch in the phase 1 of the AP is much more accentuated in the epicardium of the right ventricular outflow tract (RVOT), where the I_{to} current is more abundant, compared to the intermediate M cells and the endocardium, giving rise to more prominent I_{to}-mediated spike-and-dome AP morphology in ventricular epicardium. The more conspicuous notched configuration of the epicardial response is thought to produce a transmural voltage gradient responsible for the genesis of the J wave and J point elevation on the surface ECG (81). In healthy people, J wave is frequently small and merged in the QRS; the ST segment is isoelectric due to the absence of transmural voltage gradient during the phase 2 of the AP (Figure 5).

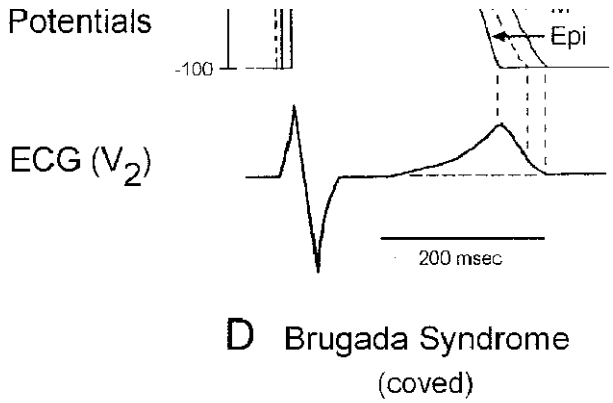

Figure 5. Normal transmembrane action potential and surface ECG *(Adapted from Antzelevitch C. J Cardiovasc Electrophysiol 2001; 12(2): 268-272).*

In Brugada patients' *loss of function* mutations of the sodium channel $Na_v1.5$ lead to a reduction of the inward sodium current (I_{Na}), living the I_{to} current unopposed in the phase 1 of the AP; this current shift accentuates the notch of the epicardium AP but not in the endocardium AP, giving reason of a greater transmural voltage gradient and a more accentuate J wave and ST segment elevation on the surface ECG. This happens because in the RVOT epicardium the I_{to} current is much more prominent

respect to the RVOT endocardium. The phase 1 of the AP is a result of al least 3 currents (I_{Na}, I_{to} e I_{Ca}); mutations of ion channels provoking an outward shift in the balance of currents are able to produce the same effect of the *loss of function* mutations of the sodium channel $Na_v1.5$.

If the epicardial repolarization continues normally, preceding the repolarization of the M-cells and of the endocardium, the T wave remains positive and the surface ECG assume a saddleback configuration (Figure 6) (82).

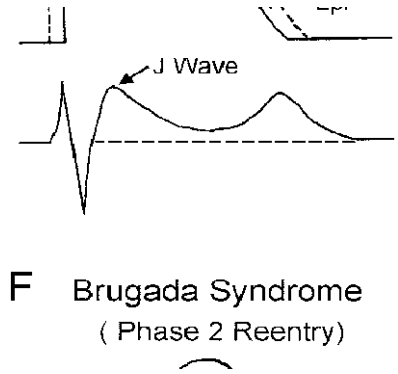

Figure 6. Action potential and surface ECG in patients with Brugada Syndrome and a Saddleback configuration *(Adapted from Antzelevitch C. J Cardiovasc Electrophysiol 2001; 12(2): 268-272).*

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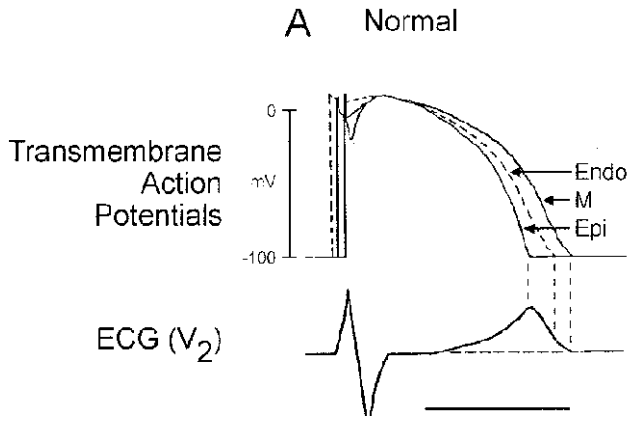


Figure 7. Action potential and surface ECG in patients with Brugada Syndrome and a coved-type configuration *(Adapted from Antzelevitch C. J Cardiovasc Electrophysiol 2001; 12(2): 268-272).*

If there is a prolongation of the epicardial AP reversing the direction of the repolarization across the right ventricular wall, the ST segment elevation is followed

by a negative T wave and the surface ECG assumes a coved type configuration (Figure 7) (82).

The current imbalance, coming from a reduction of the outward sodium or calcium current or the implementation of the potassium inward current, is responsible also for the loss of the AP dome morphology in some epicardial site, causing a marked shortening of the AP in some epicardial cell but not in all, leading to both a transmural and intra-epicardial pronounced dispersion of repolarization. Moreover, the dysfunction of the sodium channel impairs the conduction of the current impulse and creates conduction blocks. The loss of the AP dome in epicardium, the consequent shortening of the refractory period in some cells but not in all and the presence of conduction block are the basis for the micro-reentry between cells; it creates a vulnerable window during which an ectopic beat can induce a reentrant arrhythmia (Figure 8). This arrhythmogenesis mechanism is called “phase 2 reentry” and can induce VF.

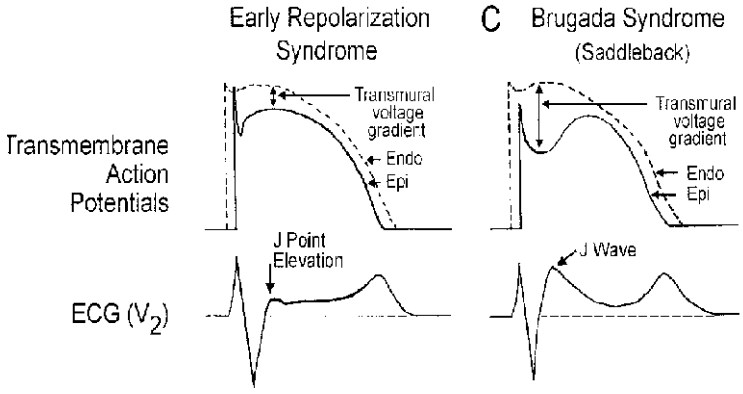


Figure 8. Loss of dome of the epicardial action potential and phase 2 reentry *(Adapted from Antzelevitch C. J Cardiovasc Electrophysiol 2001; 12(2): 268-272).*

In conclusion, Antzelevitch *et al.* demonstrated that the basis for ECG abnormalities and arrhythmogenesis in BS is an outward shift of net transmembrane current at the end of the phase 1 of the AP in the epicardium, where the I_{to} current is most

prominent, but not in the endocardium. This cause an accentuated spike and dome morphology of the AP in epicardium, a voltage gradient between epicardium and endocardium during phase 1 of the AP and in some epicardial cells also the loss of the AP dome and the abbreviation of the AP duration. There is both a voltage gradient between endocardium and epicardium and between different epicardial cells with different AP duration. Ectopic beats that find some epicardial cells in a vulnerable phase because of their short AP can induce reentrant arrhythmias and VF. The reason why only some epicardial cells lose the dome morphology in response to mutations of the ions channels proteins is a heterogeneous expression of the I_{to} current (83, 84). This hypothesis is consistent with the evidence that BS is associated with *loss of function* mutations of sodium and calcium channels and with *gain of function* mutations of potassium channels (81, 82, 85).

This fascinating theory coming from experimental studies lack of strong clinical relevant proofs and that brings to the development of other pathogenesis hypothesis.

The depolarization hypothesis

The depolarization hypothesis suggests that a conduction delay, particularly in the RVOT, is the basis of arrhythmogenesis in BS. In connection with the conduction delay, there are evidences of ultra-structural abnormalities in the right ventricle of Brugada patients that may be responsible for the presence of slow conduction areas (86). These mild structural changes, like fibrosis, are not detectable with the conventional imaging tools (echocardiography, magnetic resonance) but were found in an explanted heart or in biopsies of BS (87, 88). According to the depolarization hypothesis, the RVOT is the last to depolarize; the delay in the AP of the RVOT generates a gradient from the most positive RV and the RVOT that generates an ST-segment elevation in the right precordial leads. The gradient is reversed during

repolarisation resulting in a negative T wave on the surface ECG of the same right precordial leads (69).

Most of the evidences supporting this theory come from clinical studies. The first evidence comes from Nagasa *et al*: they found abnormal electrograms with late potentials after QRS recording from the epicardium of the RVOT (89). The report from Nademanee *et al* gave strong clinical evidence of this hypothesis; they studied 9 patients with BS and recurrent VF; they recorded abnormal prolonged ventricular electrograms and abnormal low voltage fractionated electrograms in the epicardium of the RVOT of these patients. The ablations of these potential brought to ECG normalisation and rendered ventricular arrhythmias no more inducible (90).

Both the theories agree about the origin of the ventricular arrhythmias in BS, coming surely from the RVOT. Although in the past decades many studies brought new insight in the pathogenesis and arrhythmogenesis of BS, both the repolarization and the depolarization hypothesis are not able to fully explain the disease.

Clinical presentation

BS is characterised by the presence of a typical ECG pattern and malignant ventricular tachyarrhythmia. Syncope, agonal respiration and cardiac arrest are the typical clinical manifestations. The first two symptoms are caused by self-terminating ventricular arrhythmias; cardiac arrest is due to VF. Patients may remain asymptomatic for a long period and in some cases cardiac arrest due to VF is the first and only clinical manifestation of the disease. Brugada patients are relatively young, between 20 and 40 years old; there is a 10-fold higher prevalence in male than in female, despite an autosomal dominant inheritance pattern. BS is responsible for 4-12% of all SCA and for 20% of SCD in patients with structurally

normal heart. The mean age of patient presenting with VF is 41 ± 15 years. Arrhythmic events occur predominantly in men (5.5-fold risk of SCD compared with women), during the night, at rest or while asleep, ventricular arrhythmias are not triggered by sport activity. Patients may report palpitations: typically, these are due to atrial fibrillation, which has a higher prevalence (11-14%)in Brugada patients (62, 64, 65, 69).

Diagnosis

Diagnostic Criteria

The last version of the diagnostic criteria was published in 2013 in the consensus statement on inherited primary cardiac arrhythmias syndromes and in 2015 in the guidelines for the management of patients with ventricular arrhythmias and prevention of SCD. They affirmed that "BS is diagnosed in patients with ST- segment elevation with type 1 morphology ≥2 mm in ≥1 lead among the right precordial leads V1, V2, positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs. BS is diagnosed in patients with type 2 or type 3 ST-segment elevation in ≥1 lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type I ECG morphology" (11, 56). The J-wave syndrome expert consensus conference held in Shanghai in 2017 recommend that when a type 1 Brugada ECG pattern is unmasked using a provocative drug test, the diagnosis of BS should be made only if there are 1 of the following criteria: documented VF or polymorphic VT, syncope of probable arrhythmic cause, a family history of SCD at 45 years old with negative autopsy, coved-type ECGs in family members, or nocturnal agonal respiration. They also

proposed a diagnostic score system, called the "Proposed Shanghai Brugada Syndrome Score"; the diagnosis of BS is probable/definite with ≥ 3.5 points, possible with 2-3 points and non diagnostic if there are less than 2 point. In Table 2 we reported the clinical variable and the corresponding points (70).

Table 2. Proposed Shanghai Score System for diagnosis of Brugada syndrome *(modified from Antzelevitch et al. Europace 2017; 19(4): 665-94).*

CLINICAL VARIABLES	POINTS
I. ECG (12-Lead/Ambulatory)*	
A. Spontaneous type 1 Brugada ECG pattern at nominal or high leads	3.5
B. Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
C. Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	2
II. Clinical History**	
A. Unexplained cardiac arrest or documented VF/ polymorphic VT	3
B. Nocturnal agonal respirations	2
C. Suspected arrhythmic syncope	2
D. Syncope of unclear mechanism/unclear etiology	1
E. Atrial flutter/fibrillation in patients < 30 years without alternative etiology	0.5
III. Family History**	
A. First- or second-degree relative with definite BS	2
B. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative	1
C. Unexplained SCD < 45 years in first- or second- degree relative with negative autopsy	0.5
IV. Genetic Test Result	
A. Probable pathogenic mutation in BS susceptibility gene	0.5

*Only award points once for highest score within this category. One item from this category must apply. **Only award points once for highest score within this category. BS=Brugada syndrome; SCD= sudden cardiac death; VF= ventricular fibrillation; VT=ventricular tachycardia.

Pharmacologic test

The ECG alterations in Brugada patients are dynamic and concealed, so they need to be unmasked with a provocative test. At the basis of the electrocardiographic pattern there is a current imbalance during the AP with a reduction of the net outward current. Provocative pharmacological test is for this reason performed with sodium channel blockers (ajmaline, flecainide, procainamide, pilsicanide), which accentuate the genetic defect. It is recommended in patients where there is a clinical suspicion of BS in the absence of a spontaneous type 1 ECG; it should not be performed in case of asymptomatic patients with a spontaneous type 1 ECG because of the lack of additional diagnostic value. The test is considered positive a type 1 Brugada ECG pattern is induced; it must be interrupted in case of sustained ventricular arrhythmias or widening of the QRS > 130% of the baseline value. Because of the possibility of severe complications (ventricular arrhythmias, mechanoelectrical dissociation), the test should be performed und close monitoring with continuous ECG monitoring and full equipment for resuscitation (62, 64, 70).

Genetic Test

Because of the complex and heterogeneous genetic background, genetic test has a very limited role in the diagnosis of BS. SCN5A variants account only for 18%-28% of patients and other 17 genes are associated with BS. As previous reported, genetic alone cannot explain the phenotype. Probst *et al.* analysed 13 families with SCN5A mutation and the genotype did not co-segregate with the phenotype; some family members showing BS phenotype did not have the familial SCN5A mutations and mutation carriers do not have a diagnostic Brugada ECG (91). As reported in the HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies in 2011, genetic test is not involved in the diagnosis of the disease. They recommend to do genetic test in particular situations: 1) genetic testing can be useful for any patient in whom a cardiologist has

established a clinical index of suspicion for BS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype; 2) genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern; 3) mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BS-causative mutation in an index case (92). In asymptomatic mutation carriers it is very important to perform a strict follow-up and to advised the subject to prevent and correct hypokalaemia, to promptly treat a fever >38° by antipyretic therapy, and to use caution in taking antiarrhythmic drugs known to worsen ECG abnormalities and potentially trigger VT/VF in BS (92).

Differential diagnosis

Before confirming the diagnosis of BS, other causes of ST elevation in the right precordial lead should be excluded. The J-wave syndrome expert consensus conference proposes a list of condition that must be considered as alternative diagnosis when we are facing patients with St-segment elevation in right precordial leads. These are: atypical right bundle branch block; ventricular hypertrophy; early repolarization (especially in athletes); acute pericarditis/myocarditis; acute myocardial ischemia or infarction (especially of the right ventricle); pulmonary thromboembolism; Prinzmetal angina; dissecting aortic aneurysm; central and autonomic nervous system abnormalities; Duchenne muscular dystrophy; Friedreich ataxia; spinobulbar muscular atrophy; myotonic dystrophy; arrhythmogenic right ventricular cardiomyopathy (ARVC); mechanical compression of the right ventricular outflow tract (e.g. pectus excavatum, mediastinal tumor, hemopericardium); hypothermia; post-defibrillation ECG (70). Particularly challenging is the differential diagnosis with ARVC. ARVC is a genetic cardiomyopathy that predominantly affects the right ventricle. It is characterized pathologically by RV myocardial atrophy with

fibro- fatty replacement, which acts as a substrate of ventricular electric instability leading to malignant ventricular tachyarrhythmia. Molecular genetic has provided new insights in understanding the pathophysiology of ARVC, showing that it is a desmosomal disease resulting from defective cell adhesion proteins (44). There are similarities in the phenotypic expression of the two diseases. Both of them affect the RVOT, manifest with syncope and cardiac arrest due to ventricular tachycardia and presents typical ECG abnormalities in the right precordial leads like T wave inversion or conduction disturbances. Particularly in the concealed phase of ARVC, characterized by no or subtle right ventricular structural changes, it could be hard to distinguish the two clinical entities (70).

Risk stratification

BS is a channelopathy associated with increased risk of SCD among young people and ICD is the only effective therapeutic strategy to prevent this tragic event. Risk stratification is challenging particularly in asymptomatic patients, where the risk of malignant arrhythmic events during follow-up is very low but not zero and sudden death could be the first and only manifestation of the disease. Because of the low prevalence of the disease and the low events rate, it is very difficult to find strong predictors of fatal arrhythmic outcome. Considering the relative high incidence of complications of ICD therapy and its negative impact on quality of life and morbidity, the decision whether to implant an ICD in a Brugada patient should be precede by an accurate risk assessment, balancing possible advantages and complications.

Clinical manifestations: syncope, cardiac arrest and asymptomatic patients

Cardiac arrest survivor presenting with a Brugada ECG pattern are at very high risk of fatal events recurrence during follow-up; in this particular subset of patient ICD implantation has a Class I indication (70). Data from different studies support this recommendation. The rate of recurrent arrhythmic events among cardiac arrest survivors was 7.7% per year in the FINGER registry (93); in patients in whom the ICD therapy indication was aborted SCD, appropriate device therapy rate at 7 years was 44% in the study from Conte *et al* (94) and at 10 years was 48% in the study from Sacher *et al* (95).

Syncope is a typical clinical manifestation of BS but its underling mechanism could be different and also its prognostic value (96). Non-arrhythmic syncope is normally of vaso-vagal origin, presenting with prodromes and with a recognised trigger; patients with this type of syncope have a good prognosis. On the contrary in case of malignant syncope, neither prodromes nor specific trigger are present, suggesting that the syncope is due to a self-terminating ventricular arrhythmia. In this case the prognosis is unfavourable and there is a strong indication for ICD implantation (70). The annual cardiac event rate of patients with syncope was 1.9% in the FINGER study (93) and 3% in the study from Delise *et al* (97); in many studies syncope was found to be an independent predictor of malignant arrhythmic events during follow-up (93, 95, 97-99).

All the studies above mentioned confirm the good prognosis of patients presenting with a Brugada ECG pattern without typical symptoms. In asymptomatic patients the cardiac event rate per year is very low and varies between was 0.5% and 1% (93, 95, 97).

Established that in case of a clinical presentation with cardiac arrest, ventricular arrhythmia and syncope there is a clear indication for ICD implantation because of a high rate of recurrences of cardiac arrhythmic events during follow-up, the decision for a prophylactic ICD in asymptomatic subject is still a matter of debate. Many

efforts have been made in finding predictors of a poor arrhythmic outcome in this low-risk class of patients, analysing the prognostic value of gender, family history, genetic predisposition, ECG abnormalities and inducibility at electrophysiological study (EPS).

Gender, family history and genetic predisposition

In the Finger study they proved that gender, family history of SCD, and presence of a mutation in the *SCN5A* gene have no predictive value (93). Also Delise *et al.* found that male gender and family history of SCD conferred an increased risk, but they do not reach a statistical significant power (97). Until now, only one study has demonstrated that some SCN5A mutations leading to premature truncation of the protein bring to a more severe phenotype than missense mutations of the same protein (100). This is an important evidence of the possible role of genetic testing in risk stratification in BS. Nevertheless, there are insufficient data to allow the use of routinely genetic testing for prognostic use.

Electrophysiological study

The role of EPS in risk stratification in BS is still under debate. The study from Brugada *et al.* demonstrated that in Brugada patients with no history of previous cardiac arrest the inducibility of a sustained ventricular arrhythmia was a predictor of events in the multivariate analysis (99). On the contrary, in the FINGER study inducibility of sustained ventricular arrhythmia during EPS was not predictive of arrhythmic events (93). The study of Delise *et al.* highlighted the role of EPS in the risk stratification as an addiction variable that should be considered only together with other clinical risk factors; particularly they found that EPS has a 100% negative predictive value, so it could help in identify subjects at low risk (97). The PRELUDE study is a prospective registry, designed to assess the predictive accuracy of inducibility of sustained VT/VF in Brugada patient with no previous history of

sustained ventricular arrhythmia/cardiac arrest; they found that inducibility at EPS was not a predictors of events during follow-up. Of the contrary, they demonstrated that a ventricular refractory period < 200 ms is a strong predictors of arrhythmic events during follow-up (98). The discrepancy between the above-mentioned studies relies probably on two major factors: the differences in the programmed ventricular stimulation protocol (number of extrastimuli, site of stimulation) and in the basal population.

Repolarization and depolarization abnormalities

Among all ECG abnormalities, the presence of a spontaneous type I Brugada ECG pattern at the time of the diagnosis is the most powerful predictor of arrhythmic events during follow-up (93, 97, 98). In addition, both depolarization and repolarization ECG abnormalities offer the potential to refine the risk stratification in BS and their prognostic value have previously reported. Conduction abnormalities like the prolongation of PR interval (101), the increase of QRS duration (102, 103), as well as the presence of left anterior fascicular block (101) and right bundle branch block (104) confer an increased arrhythmic risk. In the PRELUDE study, not only the presence of a spontaneous type I ECG but also the evidence of a fragmented QRS (defined as 2 or more spikes within the QRS complex in leads V1 to V3) was significant predictors of arrhythmias during follow-up (98). Recently, it has been demonstrated that the presence of a wide and/or large S wave in lead I is an independent predictor of ventricular arrhythmias during follow-up (105). Repolarization abnormalities found to be markers of increased arrhythmic risk are the prolongation of QT interval (106, 107), the presence of T-waves alternans (107) and the pattern of early repolarization in the inferior and lateral leads (106, 108-110).

Therapy

Treatment options in BS include lifestyle changes, antiarrhythmic drug therapy, catheter ablation of the RVOT and ICD implantation. In figure 9 are graphically represented the recommendations for management and treatment of Brugada patients.

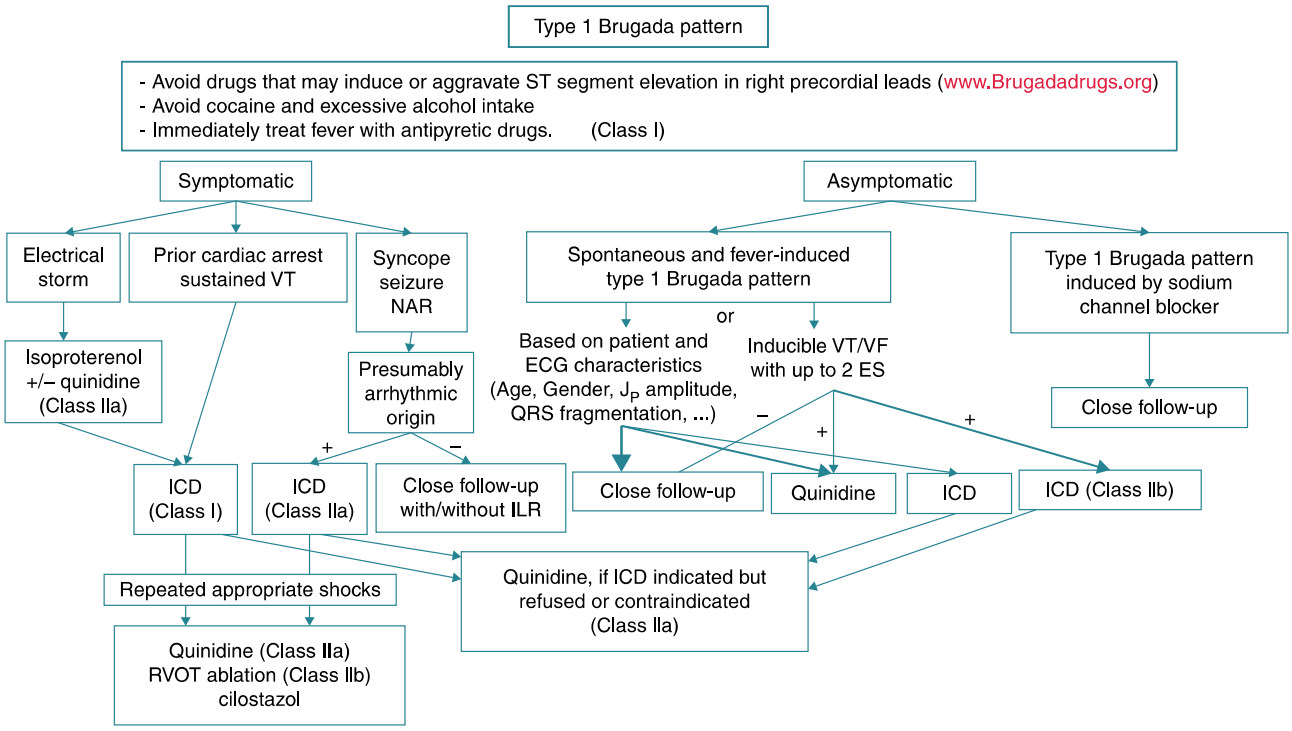


Figure 9. Recommendations for therapy according to the J-Wave syndromes expert consensus conference report *(modified from Antzelevitch et al. Europace 2017; 19(4): 665-94).*

Lifestyle changes include prompt treatment of fever and avoidance of drugs and toxins that can exacerbate the typical ECG abnormalities and induce VT (70).

Among antiarrhythmic drugs, amiodarone and Class IC agents are respectively ineffective and contraindicated. The only antiarrhythmic drug able to normalize ECG and reduce ventricular arrhythmia is quinidine, because of its ability to inhibit the I_{to} current; both experimental models and clinical data support the effectiveness of quinidine in this setting. Unfortunately, selective inhibitors of the I_{to} current are not available. Quinidine is indicated in patients with recurrent appropriate ICD

interventions and if ICD is refused or contraindicated (70). In case of electrical storm, beta-adrenergic agents such as isoproterenol are useful (70).

Different studies reported the efficacy of ablation of late and fragmented epicardial potentials of the RVOT in reducing arrhythmic recurrences and normalising the ECG pattern (90, 116). Ablation may de considered in case of recurrent ICD shocks (70).

ICD is the only proven life saving therapy in patients with BS at high risk for SCD. The available literature and the clinical experience of the task force members of the Shanghai conference allow the following recommendation for ICD therapy. ICD implantation is recommended in case of: 1) aborted SCD or documented VT/VT (Class I), 2) syncope likely caused by VT/VF in patients with a diagnostic Brugada ECG (Class IIa), 3) inducibility of VF at PVS (Class IIb).

ICD therapy is not free from complication, given the considerable incidence of adverse events like inappropriate ICD interventions and lead failure. In the study from Sacher *et al.*, rates of inappropriate shock and lead failure at 10 years were 37% and 29%, respectively (95). Conte *et al.* found that 33 (18.7%) patients had inappropriate shocks and 28 (15.9%) patients had device-related complications (93).

Kennedy Disease

Spinal and bulbar muscular atrophy, also known as Kennedy's disease (KD), is a rare, slowly progressive, neuromuscular disorder. It is caused by a mutation in the first exon of the androgen steroid hormone receptor (AR) gene on chromosome X. The accumulation of the pathogenic AR proteins in the nucleus of motor neurons is central to the pathogenesis of this disease. AR is expressed ubiquitously and non-neurological symptoms are common in KD. Of note, nuclear accumulation of the pathogenic AR was observed in autopsied myocardium (117).

A population of affected 144 patients from Japan was evaluated to clarify myocardial involvement in KD and it was reported an increased incidence of Brugada-type ECG changes. Among ECG abnormalities, a Brugada type ECG was detected in 17 patients (11.8%) and particularly type 1 was found in 6 subjects, type 2 in 7 subjects, and type 3 in 4 subjects. Moreover, 2 subjects had symptomatic BS and both of them experienced SCD. Genetic test was performed but no gene mutation associated with BS was found. Interesting, a marked decrease in messenger RNA levels of SCN5A was demonstrated in these 17 affected patients.

ICD implantation: efficacy and safety

ICD is the only proved life-saving treatment for patients with cardiomyopathies and channelopathies at high risk for SCD; nevertheless, it is not free from complications and it might lead to a significant morbidity and reduced quality of life, particularly in young patients (118). There is a strong agreement for ICD implantation in secondary prevention, i.e. in patients who survived a cardiac arrest (29, 41, 57, 93-95); whether to implant or not an ICD in patients with an arrhythmogenic cardiomyopathies and no previous history of aborted SCD is still a matter of debate. Risk stratification is challenging in young people with cardiac diseases at risk for SCD, because it allowed the identification of patients with a high probability of a malignant arrhythmic outcome that are eligible for ICD implantation.

ICD efficacy is primary due to its ability in terminating VF and VT with delivery of antitachycardia overdrive pacing (ATP) or shock. VF always bring to sudden death if not interrupted; on the contrary, VT could also be hemodynamic well tolerated and could terminate spontaneously or with pharmacological therapy, not necessarily leading to fatal VF. ICD interventions against VF are always lives saving, while ICD interventions against VT, although appropriate, are not.

ICD-related morbidity is mainly due to device related complications at the time of implant or during follow-up and to inappropriate ICD interventions (118).

Complications during ICD implantation procedure include pneumothorax, pocket haematoma, ventricular lead perforation with or without haemopericardium, catheter dislodgment and thromboembolic events (118).

Complications that may occur during follow-up are pocket haematoma, non septic pocket decubitus (Figure 10), device infection, lead dislodgement, cardiac lead perforation, lead failure/lead fracture and generator malfunction.

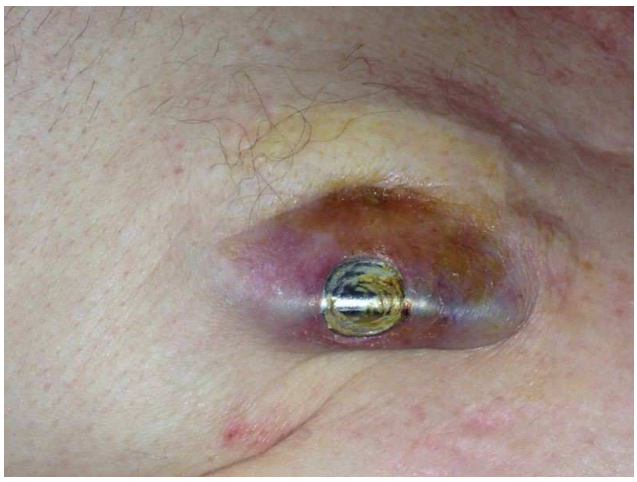


Figure 10. Pocket decubitus with skin erosion and exposure of the device.

Some of these adverse events could be treated with medical therapy, but in most cases they need a surgical revision of the system. In the study from Olde Nordkamp et al lead failure was the most frequent ICD-related complications (119); the treatment consisted in a surgical intervention for lead extraction and a repositioning of a new system (Figure 11). Lead failure can be completely asymptomatic and detected during routine device control as variation of more than 50% of pacing threshold or catheter impedance respects the normal patient value; in some cases it manifest as a inappropriate ICD interventions due to oversensing. Also lead dislodgment or cardiac lead perforation may present with inappropriate ICD

interventions or may be asymptomatic; cardiac lead perforation may also be associated with hemopericardium with cardiac tamponade, a serious and sometimes fatal event. In both cases lead repositioning is necessary.

Figure 11. Ventricular ICD lead after extraction with evidence of fibrosis.

Pocket hematoma can be managed conservatively but in some cases pocket revision is necessary to find the bleeding source.

Pocket decubitus and device infection could be very dangerous and are correlated with long hospital stay; in both cases extraction of all the system is needed and the repositioning of a new device is possible only after antibiotic therapy when no more sign of active infection is present (118).

Inappropriate ICD intervention is defined as an ICD shock delivered not in response to VF or VT. The most frequent causes are 1) supraventricular arrhythmias such as sinus tachycardia or atrial fibrillation, 2) oversensing both of cardiac signals and of extra cardiac signals like myopotentials, 3) lead failure. In young patients the type of trigger of the inappropriate intervention depends on the life style and the

underlying pathology; in HCM and in LQTS oversensing of the T wave is one of the most frequent cause of inappropriate shock. In active patients, sinus tachycardia and oversensing of myopotential are also important trigger. The management of this complication consist first in device reprogramming (118). In the MADIT-RIT trial conducted in patients with ICD for primary prevention because of ischemic disease or DCM, different types of ICD programming were tested. This study demonstrated that a high minimum threshold for therapy and long detection time were associated with a reduce incidence of inappropriate ICD interventions (120).

AIMS OF THE STUDIES

BS is a leading cause of SCD in young people. Molecular genetic has provided new insights in understanding the pathophysiology of the disease, but its real course is still unpredictable and risk stratification is challenging for this patients. The only therapy providing life-saving protection by effectively terminating life-threatening arrhythmic episodes is ICD. However young individuals with an inherited arrhythmic cardiomyopathy like BS are likely to survive for many decades, living a normal life and some even practice competitive sports activity; this condition increases the risk of inappropriate shocks and lead-related complications, which might lead to morbidity and reduce the quality.

The research project included three different studies that were performed during the four years of the PhD program.

The purpose of our first study was to assess the prognostic value of clinical and electrocardiographic parameters in patients with a Brugada-like ECG pattern (either spontaneous or drug-induced type-1). We expected to get new insights about risk stratification in BS, using a non-invasive simple exam such as ECG.

The purpose of our second study was to evaluate the balance between the efficacy of ICD in preventing SCD and the risk of ICD-related complications in young individuals (18-35 year-old) with different structural cardiomyopathies and primary electrical heart diseases (including BS), during a long-term follow-up.

The third study focused on the prevalence of a Brugada ECG pattern in patients with KD. Although an overt cardiomyopathy has not been identified in KD, an increased incidence of Brugada-type ECG changes was previously reported in a large affected population from Japan (where the prevalence of Brugada ECG pattern is high) (117). The aim of our third study, which was carried out in collaboration with the Department of Neurosciences of the University of Padova, was to determine the prevalence of the Brugada ECG pattern in a large Italian cohort of patients with KD.

METHODS

First study: prognostic value of ECG abnormalities in Brugada Syndrome

Study population

We conducted a multicentre prospective study from 1995 to 2015 in 3 medical centres of the Veneto Region of Italy (the University Hospital of Padova, the General Hospital of Conegliano and the General Hospital of Mestre). We enrolled 272 consecutive patients presenting with a spontaneous or drug-induced type 1 Brugada ECG pattern (*coved-type)*, according to the Brugada diagnostic criteria available at the time of the diagnosis (56, 62, 64).

For each patient we collected the following data: age at the diagnosis, sex, physical examination, personal and family medical history, baseline ECG, provocative test results and echocardiography. The family history was obtained at the first clinical evaluation and was considered positive if at least 1 first-degree family member showed type 1 Brugada ECG pattern or died suddenly before the age of 40 year-old in males and 50 year-old in females in the absence of known heart disease. Syncope was defined as a non-traumatic and transient loss of consciousness. Other important clinical variables collected in this study include the history of cardiac arrest/aborted sudden death and of atrial fibrillation.

Some patients underwent electrophysiology study (EPS) and other ICD implantation, according to the best clinical practice and to the current available guidelines.

Patients with structural cardiac abnormalities, on-going ischemia, metabolic or electrolytic disorders mimicking ECG Brugada pattern were not enrolled in this study. The study was approved by the institutional review board and was conducted in compliance with the principles of outlined in the Declaration of Helsinki. All patients gave their informed consent.

Electrocardiographic analysis

For every patient a 12 lead ECG were recorded at the time of the diagnosis, when no antiarrhythmic drug therapy was assumed. Three experienced electrophysiologists blinded to patients and clinical presentation evaluated all ECGs (F.M.; M.S.; M.T.). In case of disagreement, a fourth cardiologist was consulted. The ECGs were recorded at 25 mm/s of paper speed, 1 mV/10 mm gain and 0.05-150 Hz filter.

Type 1 (*coved-type*) ECG was defined as a prominent coved ST-segment elevation displaying J wave amplitude or ST-segment elevation ≥ 2 mm (0.2 mV) followed by a negative T wave with little or no isoelectric separation in the right precordial leads (V1-V3) positioned in the 2nd, 3rd or 4th intercostal space. Type 2 (*saddleback-type*) ECG has a J point elevation ≥ 2 mm, followed by ST-segment elevation ≥ 1 mm above the baseline, followed by a positive or biphasic T-wave. Type 3 has either a saddleback or coved appearance with an ST-segment elevation of <1 mm. The maximal ST-segment elevation was measured at the J point (ST_J) in leads V1 to V3.

The following basal ECG characteristics were analysed: heart rate, PQ, QRS and QT intervals, the presence of conduction disturbances, the amplitude and duration of S wave in the lead I, II or III, and the presence of an early repolarization pattern in infero-lateral leads and of QRS fragmentation in leads V1 to V3.

The heart rate, the PQ interval and the QRS and corrected QT duration were measured in lead II and V6. A PQ interval > 200 ms and a QRS interval > 120 ms were considered pathological (121). The QT interval was corrected for rate by the Bazette's formula. Right bundle branch block, left bundle branch block, left anterior fascicular block, and left posterior fascicular block were defined in accordance with current guidelines (121). The presence of an S-wave ≥ 0.1 mV and/or > 40 ms in leads I, II, and III was examined as described previously (105). Early repolarization pattern was defined as an elevation of the J-point of at least 1 mm above the baseline level in at least 2 consecutive leads, either as QRS interval slurring or notching in the inferior (II, III, aVF) or lateral (I, aVL, and V4 to V6) leads (70, 109,

110). Fragmented QRS was defined as the presence of 2 or more spikes within the QRS complex, as described previously (98).

Provocative test, electrophysiological study and ICD implantation

All patients where treated according to the current guidelines and to the best clinical practice.

Provocative test with ajmaline (1 mg/kg in 5-10 minutes) or flecainiede (2 mg/kg in 5 minutes) was performed in patients presenting with a spontaneous type 2 or 3 Brugada ECG pattern during continuous 12-lead ECG and blood pressure monitoring. The test was considered positive if a type 2 or type 3 ECG converted to type 1 after the administration of the drug, either in conventional leads V1 to V3 or at leads V1 and V2 positioned over the third intercostal space (11, 56, 70).

EPS was performed with risk stratification purpose in accordance with the current available guidelines (56, 62, 64). However, in all cases, the protocol included baseline AH and HV intervals and ventricular premature stimulation at the apex and outflow tract of the right ventricle at 2 drive cycle lengths (600 and 400 ms) delivering up to 3 ventricular extrastimuli with minimum coupling interval of 200 ms (56). The test was considered positive if a sustained VF or VT lasting for >30 seconds or requiring termination because of hemodynamic compromise was induced. Inducibility at PVS was deemed a proper indication for ICD implantation (56).

High-risk patients with a previous history of cardiac arrest/aborted sudden death underwent directly ICD implantation for secondary prevention.

Follow up

Patients underwent serial outpatient visits or telephonic interviews to determine whether they experienced any adverse event during follow-up. The primary outcome of the study was the index combined endpoint of major arrhythmic events which included SCD, cardiac arrest due to VF and appropriate ICD intervention. SCD

was defined as any natural death occurring instantaneously or within 60 minutes from symptoms onset. Appropriate ICD intervention was defined as an ICD discharge delivered in response to a ventricular tachyarrhythmia and documented by stored intracardiac ECG data.

Statistical analysis

Categorical differences between groups were evaluated by using the X^2 test or the Fisher exact test, as appropriate. Continuous variables were expressed as mean ± standard deviation or median with 25 to 75 percentiles for normally distributed and skewed variables, respectively and compared with Student *t* test or Wilcoxon rank sum test, as appropriate. Normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. The mean event rate per year was evaluated by the number of events occurring during the follow-up divided by the number of patients multiplied by the average duration of follow-up. Event-free survival curves were drawn with the Kaplan-Meier method and compared by using the logrank test. Patients were censored at the time of their first event or at the time of their last clinical follow-up. Variables with a p-value <0.15 at univariate analysis were also entered into the multivariate model. A 2-tailed P<0.05 was considered statistically significant. All analyses were performed using SPSS 18 (SPSS Inc; Chicago, IL).

Second study: risk-benefit ratio of implantable cardioverter defibrillator (ICD) in young patients with cardiomyopathies and channelopathies

Study population

The study population included 96 consecutive patients with structural cardiomyopathies or primary electrical disorders (channelopathies) referred to our Department for ICD implantation between January 1997 and December 2013, who were 18-35 year-old at the time of the procedure. Baseline clinical (including age, sex, body mass index (BMI), type of underlying cardiomyopathy, clinical history) and ICD related data including type of ICD (i.e. single or dual-chamber) and type of lead (i.e. single or dual coil and active or passive fixation) at the time of implantation were collected. BMI was calculated as weight in kilograms divided by height in meters squared. Patients were considered underweight if the BMI was less than the 5‰ in patients younger than 20 years old and less than 18.5 in those 20 years old or older (122). The institutional review board approved the study and all patients gave their informed consent.

ICD implantation

Experienced electrophysiologists performed all implantation procedures via the left subclavian vein in the subcutaneous pectoral region. Electrical parameters, including, sensing, impedance and pacing threshold were recorded at the end of the implant. A routine chest radiography and echocardiography were performed the day after the procedure to rule out complications. All devices were capable of ATP, antibradycardia pacing, delivering shock therapy and were able to record and store intracardiac electrograms before and after the therapy was delivered, thus allowing for correct classification of the treated arrhythmia. The rate cut-off for detection of VF or VT and activation of ATP was set at the discretion of managing electrophysiologist to avoid inappropriate ICD intervention and to guarantee

successful therapy of ventricular tachyarrhythmias. Secondary prevention was defined as ICD implant after resuscitated cardiac arrest or documented sustained VT/VF. The absence of a secondary prevention indication defined a primary prevention.

Follow-up

The follow-up started 24 hours after ICD implantation and data were obtained prospectively during regular outpatient visits at 1 month after implant and then at 3 to 6 months intervals. Routine ICD interrogation and ECG recording at the time of symptoms were used to document the occurrence of spontaneous VT during follow-up. At each scheduled or unscheduled visit, the pocket was assessed, the device storage was checked for delivered therapy (appropriate/inappropriate), and the integrity and appropriate functioning of the pacing system were proved. The study end points were cardiac mortality, appropriate ICD intervention, inappropriate ICD intervention and device-related complications. Adverse ICD-related events were defined as the occurrence of either an inappropriate ICD intervention or a device-related complication requiring surgical revision occurring more than 24h after implantation. Complications occurring within 24h after the procedure (i.e. pneumothorax, hemothorax and acute cardiac perforation) were excluded from the analysis.

Definitions of events

Cardiac mortality was defined as SCD, death from end-stage heart failure, and heart transplantation. Patients undergoing heart transplantation were censored at the time of the procedure. Appropriate ICD interventions were defined as a device shock or ATP delivered in response to a sustained ventricular tachyarrhythmia and documented by stored intracardiac ECG data. VF or ventricular flutter were defined as irregular or regular tachycardia with regard to polarity, amplitude, morphology,

and sequence of intracardiac electrograms, with a cycle length of 240 ms or less. VT was defined as regular tachycardia with a mean cycle length longer than 240 ms. Intervention was considered inappropriate when triggered by heart rates exceeding the programmed threshold, as a consequence of sinus tachycardia, supraventricular arrhythmias, or device or lead malfunction. All stored electrograms of arrhythmic events that triggered ICD therapy were classified as appropriate or inappropriate independently by 2 experienced electrophysiologists (F.M.; D.C.). In case of disagreement, a third electrophysiologist was consulted.

Device-related complications requiring surgical revision included: cardiac lead perforation, pocket haematoma, non-septic pocket decubitus, device infection, lead dislodgement, lead failure/lead fracture, and generator malfunction. For the purpose of this study we considered only atrial and ventricular lead perforation occurring more than 24h after implant (excluding lead perforation at the time of procedure), suspected by chest x-ray and confirmed by computed tomography (123). Pocket hematoma was defined as a palpable mass that protruded more than 2cm anterior to the device. The criteria for the surgical drainage of pocket hematoma included progressive enlargement not expected to resolve with conservative treatment, the presence of tense swelling causing poor capillary perfusion and haematoma causing severe pain. Non-septic pocket decubitus was defined as the thinning of the skin above the generator with signs of local inflammation, such as erythema, warmth, fluctuance due to mechanical decubitus without skin perforation or evidence of device infection. Device infection was defined by the presence of local signs of inflammation including skin erosion/perforation, wound dehiscence or purulent drainage with bacterial growth wound cultures or lead vegetations detected by echocardiography or the fulfilment of modified Duke criteria for infective endocarditis (124, 125). Lead dislodgement was defined as inadequate capture and/or sensing or phrenic nerve stimulation with (macrodislocation) or without (microdislocation) a visible change in the lead position

on chest X-ray, irresolvable by device reprogramming. Lead failure, including lead fracture, was defined as a non-physiological change (≥50% as compared with chronic values) in the impedance with change in the sensing/pacing threshold (intermittent or permanent) and/or electrical noise artefacts from rapid, nonphysiological make-break potentials recorded on the sensing channel with or without visible lead fracture on chest radiography and without evidence of lead dislodgement (126, 127). Oversensing of non-cardiac potentials, such as electromagnetic interferences, were not considered lead failure for the purpose of this analysis. Generator malfunction was defined as any malfunction of the pulse generator requiring premature replacement.

Statistical analysis

Results are summarized as mean ± standard deviation or median with 25 to 75 percentiles for normally distributed and skewed variables, respectively. Normal distribution was assessed using Shapiro–Wilk test. Kaplan–Meier analysis was used to estimate the survival distributions of the end points. Start of follow-up was defined as the date of the ICD implantation. Patients were censored at the time of their first event or the time of their last clinical follow-up. The mean event rate per year was evaluated by the number of events occurring during the follow-up divided by the number of patients multiplied by the average duration of follow-up. Univariate analysis was used to determine predictors of inappropriate ICD interventions and both univariate and multivariate Cox regression analysis were used to determine predictors of device-related complications. Because of the heterogeneity of the underlying cardiac diseases, the analysis for predictors of appropriate events was not performed. Variables with a probability value <0.15 were integrated into multivariable analysis using Cox proportional-hazard models to estimate the Hazard ratio (HR) and to identify independent predictors of outcome. A

value of $P<0.05$ was considered significant. Statistics were analyzed with SPSS version 17 (SPSS Inc, Chicago, IL).

Third study: prevalence of Brugada syndrome in Kennedy's Disease

In our third study, 73 consecutive Italian patients with KD underwent a full clinical protocol including biochemical and hormonal analyses, genitourinary examination, bone metabolism and densitometry, cardiological evaluation and muscle pathology. Cardiological evaluation included clinical history, standard 12-lead ECG and standard two-dimensional Doppler echocardiography. Additionally, all patients underwent a modified ECG recording with right precordial leads placed to the third and second intercostal spaces, to increase the sensitivity for Brugada-like abnormalities. Brugada-like ST-segment and T-wave (ST-T) abnormalities in right precordial leads were classified according to the second consensus conferences on the Brugada syndrome (62). The sodium channel blocker test was not performed. All ECGs were evaluated by two experienced electrophysiologists (D.C. and M.S.).

RESULTS

First study: prognostic value of ECG abnormalities in Brugada Syndrome

Patients' characteristics

The study population consisted of 272 consecutive subjects (223 men; mean age 43±12 years), whose baseline clinical characteristics are shown in Table 3. At enrolment, 81 patients (30%) were symptomatic for arrhythmic syncope (73; 26%) or had history of cardiac arrest (8; 3%); 124 (45%) had a family history of BS or SCD and 19 patients (7%) had a history of paroxysmal atrial fibrillation. A spontaneous type 1 ECG pattern was observed in 137 patients (50%). 143 patients (52,5%) underwent EPS, and 51/143 (35%) were inducible to sustained VT or VF. 69 patients (25%) received a prophylactic ICD because of cardiac arrest (n=7), syncope (n=38), or inducibility at PVS in the absence of symptoms (n=24).

Electrocardiographic findings

ECG findings of the study population are reported in Table 3. Half of our population presented with a spontaneous type 1 ECG. Mean QRS duration was 105±25 ms in lead II and 109±15 ms in lead V2. The mean QTc interval was 402±33 ms. Left anterior fascicular block was present in 48 patients (18%), 5 patients (2%) presented a f-QRS in leads V1, V2, and V3. A first-degree AV block was present in 45 patients (16.5%); of these, 27 underwent EPS and an HV interval ≥55 msec was recorded in 21 (78%). A first-degree AV block was significantly more frequent in patients with spontaneous versus drug-induced type 1 ECG (P = 0.009) (Table 4). An infero-lateral ER pattern was observed in 9 patients (3%).

Table 3. Baseline clinical and electrocardiographic characteristics of the study population.

Clinical and ECG characteristics	Population N = 272 (%)
Age (yr; mean ± SD)	43±12
Male Gender	223 (82)
Family history	
Family history of BS	51 (19)
Family history of SCD	73 (27)
Personal history	
History of syncope	73 (26)
History of CA	8 (3)
History of syncope or CA	81 (30)
History of palpitations	51(19)
History of atrial fibrillation	19 (7)
Inducibile VT/VF at EPS	51/143 (35)
ICD recipients	69 (25)
ECG	
First degree AV block	45 (16,5)
Spontaneous type 1	137 (50)
QRS duration in D2 (ms; mean ± SD)	105±25
QRS duration in V2 (ms; mean ± SD)	109±15
QTc interval (ms; mean ± SD)	402±33
Fragmented QRS	5 (2)
Left anterior fascicular block	48 (18)
Early repolarization	9 (3)
S-wave in lead I	134 (49)
S-wave in lead II	181 (66)
S-wave in lead III	157 (58)
S1S2S3 pattern	71 (26)

Categorical variables are presented as number of patients (%). Continuous values are expressed as median with standard deviation. SD=standard deviation; BS=Brugada Syndrome; SCD=sudden cardiac death; CA=cardiac arrest; VT=Ventricular Tachycardia; VF=Ventricular fibrillation; EPS=electrophysiological Study; AV= atrio-ventricular.

Table 4. Baseline clinical and electrocardiographic characteristics of patients with and without first-degree AV block.

	Presence of first-degree AV Block n = 45 (%)	Absence of first-degree AV Block n = 227(%)	p
Age (yr)	47 (32-58)	43 (33-51)	0.27
Male Gender	37 (82)	186 (82)	1.0
Family history			
Family history of BS	13 (29)	38 (17)	0.063
Family history of SCD	17 (38)	56 (25)	0.096
Personal history			
History of syncope	11 (24)	62 (27)	0.85
History of CA	1 (2)	7 (3)	1.0
History of syncope or CA	11 (24)	70 (30)	0.33
History of palpitations	8 (18)	43 (19)	1.0
History of AF	0 (0)	2 (1)	1.0
Inducibile VT/VF at EPS	13 (48)	38 (33)	0.18
ECG			
Spontaneous type 1	31 (67)	106 (47)	0.009
QRS duration in D2 (ms)	110 (100-120)	95 (80-120)	0.042
Left anterior hemiblock	13 (29)	35 (16)	0.056
Fragmented QRS	0 (0)	4 (2)	1.0
Early repolarization	2 (4)	7 (3)	0.64
S-wave in lead I	27 (61)	107 (47)	0.10
S-wave in lead II	31 (70)	150 (66)	0.72
S-wave in lead III	25 (57)	132 (59)	0.86
S1S2S3 pattern	13 (29)	58 (26)	0.71
QTc (ms)	400 (377-421)	400 (380-420)	0.854

Categorical variables are presented as number of patients (%). Continuous values are expressed as median with 25% and 75%, respectively. AF = atrial fibrillation; AV = atrioventricular; BS = Brugada syndrome; CA = cardiac arrest; EPS=electrophysiological study; SCD = sudden cardiac arrest; VT/VF = ventricular tachycardia/ventricular fibrillation.

Follow-up

The mean follow-up period for the entire study population was 85±44 months. Seventeen patients (6.3%) experienced at least 1 arrhythmic event (annual incidence rate =0.9%), which consisted of SCD in 4 (1.4%) and appropriate ICD interventions on VF in 13 (5%). Six patients (8.7%) experienced device-related complications including lead failure (n=2), lead dislocations (n=1) and infections (n=3) requiring surgical revision. Compared with patients with an uneventful outcome, those who experienced arrhythmic events during follow-up had significantly more often a history of CA or syncope (P < 0.001) and were more likely inducible at EPS (P = 0.004) (Table 5). There was no significant difference between patients who did and did not have arrhythmic events during follow-up with regard to age, gender, history of palpitations or atrial fibrillation and family history for BS or SCD. Among the ECG parameters, a spontaneous type 1 ECG pattern (P =0.01) and a first-degree AV block at baseline (P <0.001) were significantly more often observed in patients with arrhythmic events (Table 5). No others ECG depolarization or repolarization abnormalities differed between the two groups (Table 5).

Predictors of Events

Kaplan-Meier analysis for event-free survival according to first-degree AV block is shown in Figure 12. Univariate and multivariate analysis for predictors of any arrhythmic events during follow-up are shown in Table 6. Univariate predictors of events included a previous history of cardiac arrest or syncope, a spontaneous type 1 ECG pattern and the presence of a first-degree AV block at baseline ECG. In a multivariate model these parameters remained significant predictors of an arrhythmic outcome (P<0.001, P = 0.04 and P = 0.002, respectively).

Table 5. Clinical characteristics of patients with and without major arrhythmic event during follow-up.

	No event N=255	Event N=17	p
Age (yr)	43 (33-53)	44 (31-50)	0.60
Male gender	207 (81)	16 (94)	0.32
Family history			
Family history of BS	46 (18)	5 (29)	0.25
Family history of SCD	66 (26)	7 (41)	0.17
Personal history			
History of syncope	63 (25)	10 (59)	0.002
History of CA	4 (2)	4 (24)	0.001
History of syncope or CA	69 (27)	12 (71)	<0.001
History of palpitations	48 (19)	3 (18)	1.0
History of AF	17 (7)	2 (12)	0.34
Inducible VT/VF at EPS	43/133 (32)	8/10 (80)	0.004
ECG			
First degree AV block	37 (15)	8 (47)	<0.001
Spontaneous type 1	126 (49)	12 (71)	0.01
QRS duration in D2 (ms)	100 (80-120)	120 (100-120)	0.06
QRS duration in V2 (ms)	100 (100-120)	120 (100-135)	0.06
Fragmented QRS	4 (2)	1 (6)	0.29
Left anterior hemiblock	45 (18)	3 (18)	1.0
Early repolarization	7 (3)	2 (12)	0.10
S-wave in D1	124 (49)	10 (59)	0.43
S-wave in D2	169 (67)	12 (71)	0.75
S-wave in D3	144 (57)	13 (77)	0.14
S1S2S3 pattern	62 (26)	7 (44)	0.11
QTC (ms)	400 (380-420)	413 (387-428)	0.35

Categorical variables are presented as number of patients (%). Continuous values are expressed as median with 25% and 75%, respectively. AV = atrioventricular; BS = Brugada syndrome; CA = cardiac arrest; EPS = electrophysiological study; SCD = sudden cardiac arrest; VT/VF = ventricular tachycardia/ventricular fibrillation.

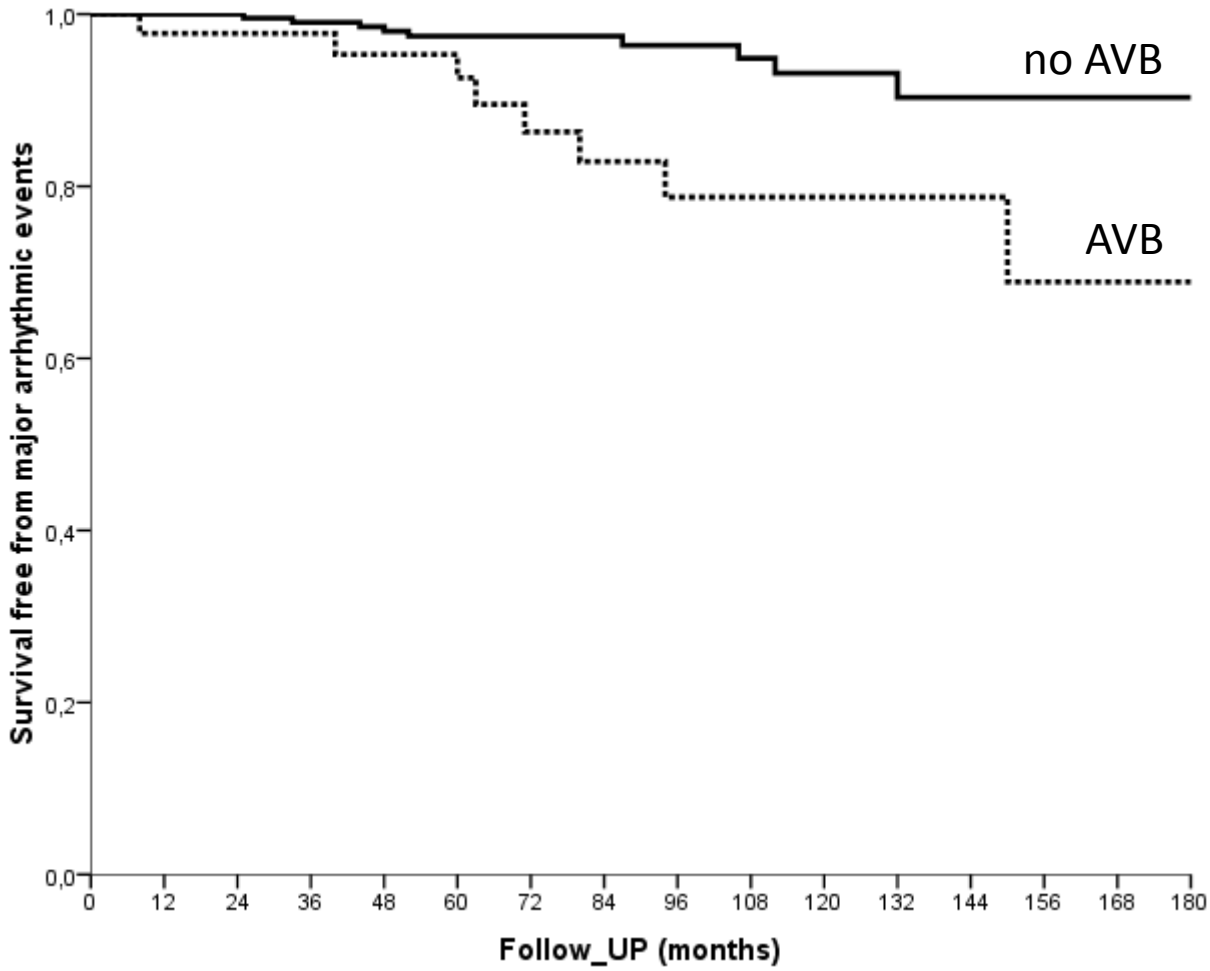


Figure 12. Kaplan-Meier analysis for event-free survival according to first-degree AV block (AVB=atrio-ventricular block).

Table 6. Univariate and multivariable predictors of major arrhythmic event during follow-up.

	Univariate analysis			**Multivariate analysis**		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
Family history of BS	1.79	0.63-5.09	0.28			
Family history of SCD	1.87	0.71-4.93	0.20			
History of syncope/CA	5.80	2.04-16.5	0.001	6.68	2.34-19.1	<0.001
Type 1 ECG pattern	1.56	0.57-4.24	0.04	1.84	1.03-4.29	0.04
First degree AV block	3.84	1.47-9.99	0.006	4.65	2.34-19.1	0.002

AV = atrioventricular; BS = Brugada syndrome; CA = cardiac arrest; SCD = sudden cardiac arrest.

Second study: risk-benefit ratio of implantable cardioverter defibrillator (ICD) in young patients with cardiomyopathies and channelopathies

Patient and ICD Characteristics

The study population included 96 consecutive patients [68 men; median age 27 years (22-32)]. Baseline clinical characteristics of the overall study population and according to the underlying cardiomyopathy are summarized in Figure 13 and Table 7. Underlying disease substrate included structural cardiomyopathy in 71 patients (74%), such as ARVC (n=35), DCM (n=17), HCM (n=15) and LVNC (n=4); and primary electrical disorders in 25 patients (26%), including BS (n=14), IVF (n=5), LQTS (n=4) and SQTS (n=2). Sixty-nine patients (71.9%) received an ICD implantation for primary prevention and 27 (28.1%) for secondary prevention. A single-chamber ICD was implanted in 83 (86.5%) patients, whereas a dual-chamber ICD was implanted in 13 (13.5%). Of the 96 ventricular leads, 58 (60.4%) had an active and 38 (39.6%) a passive fixation mechanism; 32 (33.3%) leads had a single coil and 64 (66.6%) a dual coil. Three patients received a Medtronic Sprint Fidelis (Medtronic, Inc., Minneapolis, Minnesota, USA) lead, which was subsequently withdrawn from trading while none received St. Jude Riata (St Jude Medical, Sylmar, California, USA) lead. In 55 (57.3%) patients, only one therapy zone was programmed and in the remaining patients two therapy zones. The minimal median threshold for intervention was 300 ms (300-273 ms). ATP with multiple bursts in the ventricular tachycardia zone was activated in the 41 patients with more than one therapy zone. In 31 patients with a single-therapy zone who received an ICD that supported this function, before/during charge ATP was also programmed. In 24 patients who initially received an older device with no programmable ATP in the ventricular fibrillation zone, this therapy was activated at the time of ICD replacement.

Table 7. Clinical characteristics of overall sample and according to the underlying cardiomyopathy/channelopathies.

	Overall sample 96 (%)	**ARVC 35 (36.5%)**	**DCM 17 (17.5%)**	**HCM 15 (15.6%)**	**LVNC 4 (4.2%)**	**BS 14 (14.6%)**	**LQTS 4 (4.2%)**	**SQTS 2 (2.1%)**	**IVF 5 (5.2%)**
Age (years)	27 (22-32)	27 (20-33)	30 (31-34)	28 (22-362	19 (21-25)	26 (24-31)	30 (26-31)	31	29 (26-30)
Sex (male)	68 (70.8)	25 (71,4)	10 (58,8)	9 (60)	4 (100)	14 (100)	1 (25)	1 (50)	4 (80)
BMI	24 (22-26)	24 (23-25)	25 (22-27)	26 (21-30)	23 (20-24)	24 (22-25)	23 (20-25)	24 (21-24)	24 (21-25)
Underweight status	7 (7.3)	2 (5.7)	2 (11.8)	1 (6.7)	1 (25)	0 (0)	0 (0)	0 (0)	1 (20)
Primary prevention	69 (71.9)	24 (68.6)	15 (88.2)	14 (93)	3 (75)	10 (71.4)	1 (25)	2 (100)	0 (0)
Family history of SCD	35 (36.5)	10 (28.6)	8 (47.1)	8 (53.3)	1 (25)	4 (28.6)	2 (50)	2 (100)	0 (0)
Previous syncope	40 (41.7)	13 (37.1)	1 (5,9)	6 (40)	2 (50)	9 (64,3)	4 (100)	0 (0)	5 (100)
Previous NSVT	38 (39.6)	14(40%)	8 (47,1)	8 (53,3)	2 (50)	2 (14,3)	1 (25)	0 (0)	3 (60)
Inducibility at PVS	19/30 (63.3)	9/15 (60)	0/1 (0)	/	1/1 (100)	7/10 (70)	/	2/2 (100)	0/1 (0)
LVEF < 35%*	21 (21.9)	1 (2.9)	17 (100)	1 (6.7)	2 (50)	/	/	/	/
Septum ≥30mm **	/	/	/	10 (66.7)	/	/	/	/	/
Secondary prevention	27 (28.1)	11 (31.4)	2 (11.8)	1 (6,7)	1 (25)	4 (28,6)	3 (75)	0 (0)	5 (100)
Previous cardiac arrest	17 (17.7)	5 (14.3)	1 (5.9)	0 (0)	1 (25)	4 (28.6)	2 (50)	0 (0)	4 (80)
Previous SVT	12 (12.5)	6 (17.1)	1 (5.9)	1 (6.7)	1 (25)	1 (7.1)	1 (25)	0 (0)	1 (20)

** Only for patients affected by ARVC, DCM, HCM and LVNC; ** Only for patients affected by HCM.*

Categorical variables are presented as number of patients (%). Continuous values are expressed as median with 25% and 75%, respectively. ARVC=arrhythmogenic right ventricular cardiomyopathy; DCM=dilatative cardiomyopathy; HCM=hypertrophic cardiomyopathy; LVNC=left ventricular non compaction; BS=Brugada Syndrome; LQTS=Long QT Syndrome; SQTS=Short QT Syndrome; IVF=idiopathic ventricular fibrillation; BMI=body mass index; SCD=sudden cardiac death NSVT=non sustained ventricular tachycardia; PVS=programmed ventricular stimulation; LVEF=left ventricular ejection fraction; SVT= sustained ventricular tachycardia.

Outcome

During a mean follow-up of 72.6 ± 53.3 months, 20 (20.8%) patients had a total of 38 appropriate ICD interventions and 26 (27.1%) experienced a total of 49 adverse

ICD-related events. The prevalence and distribution of patients with appropriate ICD interventions and adverse ICD-related events in the overall population and according to the underlying cardiomyopathy is shown in Figure 13. Thirty-five (36.5%) patients underwent at least one ICD replacement. In addition, one patient with end-stage HCM died because of acute heart failure and 11 (11.5%) underwent heart transplantation because of refractory heart failure.

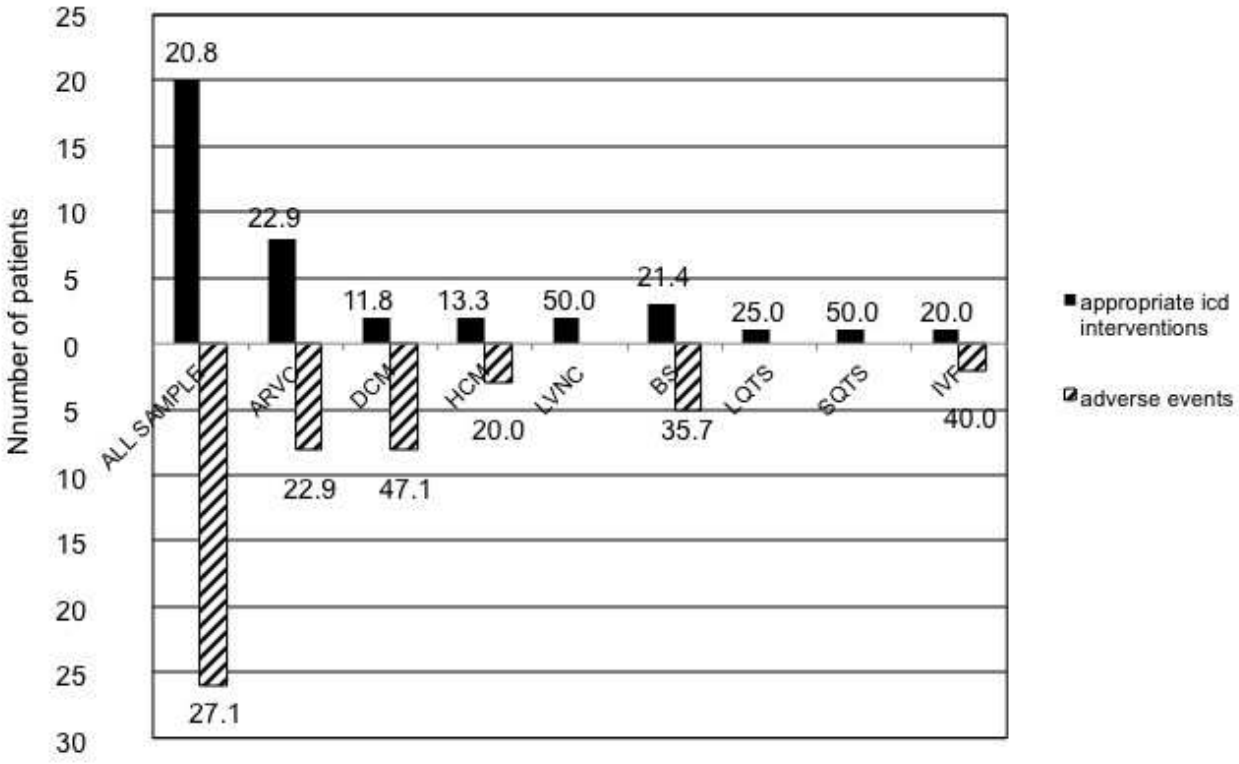


Figure 13. Prevalence and distribution of appropriate ICD interventions and adverse ICD-related events in the overall population and according to the underlying cardiomyopathy. Abbreviations as in Table 7.

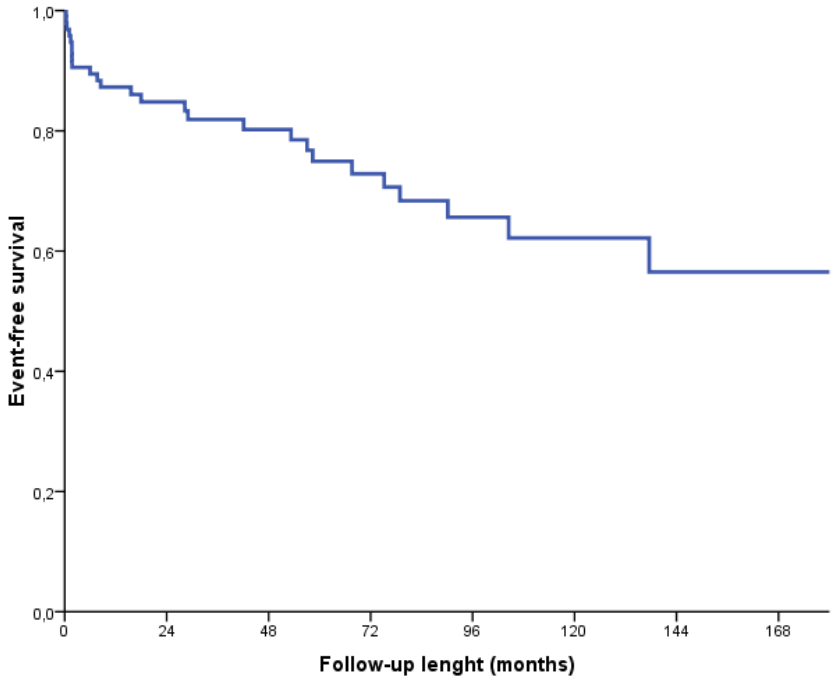
Kaplan-Meier analysis of survival free from appropriate ICD intervention and adverse ICD-related events is shown in Figure 14.

Appropriate ICD interventions

Clinical characteristics of patients with and without appropriate ICD interventions are shown in Table 8. Ten patients had a single appropriate ICD intervention and 10

had multiple interventions, including 2 patients with ventricular tachycardia storm. Sixteen patients had shocks only, 2 had only ATP interventions and 2 had both type of interventions.

A



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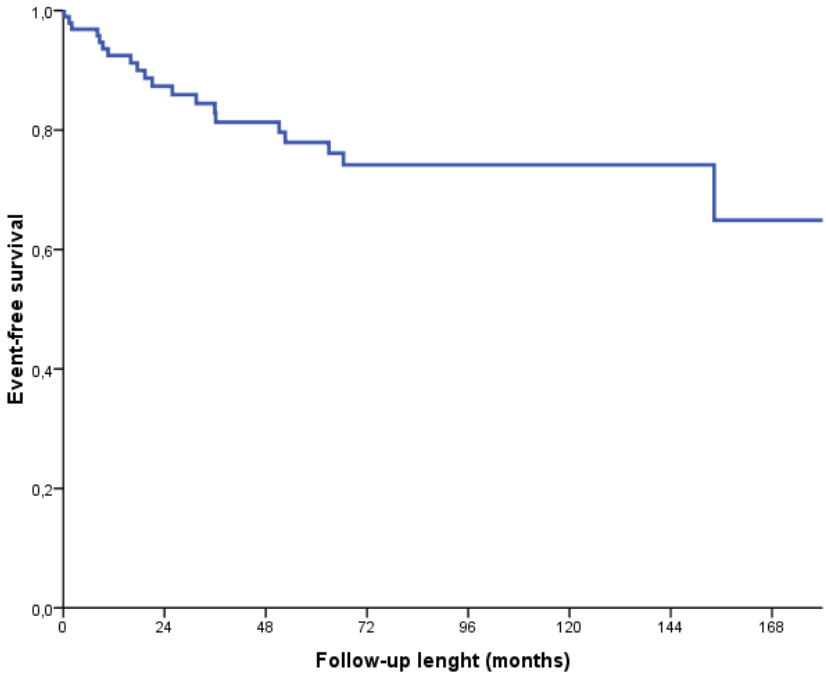

Figure 14. Kaplan-meier analysis for survival free from adverse ICD-related events (A) and appropriate ICD interventions (B).

The annual rate of first ICD intervention was 4 %/year and the average time from implantation to first appropriate ICD intervention was 31.6±35.3 months. The device successfully terminated all arrhythmic events.

Table 8. Characteristics of patients with and without appropriate ICD therapy during follow-up.

	Appropriate ICD intervention N=20 (20.8%)	**No appropriate ICD intervention N=76 (79.2%)**
Age (yrs)	29 (20-33)	26 (22-31)
Sex (male)	15 (75)	53 (69.7)
Underweight status	1 (5)	6 (7.9)
Primary prevention	11 (55)	58 (76.3)
Structural cardiomyopathy	14 (70)	57 (75)
Family history of SCD	7 (35)	28 (36.8)
Previous syncope	10 (50)	30 (39.5)
Previous NSVT	9 (45)	29 (38.2)
Inducibility at PVS (performed in 30 pt)	5/7 (71)	14/23 (61)
Previous cardiac arrest	6 (30%)	11 (14.5%)
Previous SVT	5 (25%)	7 (9.2%)
Antiarrhythmic drug therapy	17 (85)	59 (77.6)

Categorical variables are presented as number of patients (%). Continuous values are expressed as median with 25% and 75%-iles. Abbreviations as in Table 7.

A subgroup of 9 patients (9.4%) experienced at least one ICD intervention on VF or ventricular flutter with an average annual rate of first shocks on VF/ ventricular flutter of 1.7 %/y and an average time from implantation to first appropriate ICD intervention triggered by VF/ ventricular flutter of 31.5±20.5 months.

Adverse ICD-related events

Among the 49 adverse ICD-related events occurring in 26 patients (27.1%), 23 were inappropriate interventions and 26 were device-related complications requiring surgical revision. Clinical characteristics of patients with and without adverse ICD-related events are shown in Table 9. Seventeen patients had at least 1 one device-related complications, 6 received at least 1 inappropriate ICD interventions and 3 had both device-related complications and inappropriate ICD interventions. The annual rate of first adverse ICD-related event was 5.4%/year and the average time from implantation to the first adverse ICD-related adverse event was 34.2 ± 38.9 months. The annual event rate was 3.9%/year for first device-related complication and 1.7%/year for first inappropriate ICD interventions. The survival free of first ICD-related adverse event did not differ between primary and secondary prevention patients and between patients with structural cardiomyopathy and primary electrical disorder.

Reasons for the 23 inappropriate ICD interventions occurring in 9 patients (9.4%) were atrial fibrillation (n=2), supraventricular tachycardia (n=5) and lead malfunction (n=2), whereas the 26 device-related complications requiring surgical intervention occurring in 20 patients (20.8%) included ventricular lead failure/fracture (n=9), non-septic pocket decubitus (n=8), pocket infection (n=1), pocket haematoma (n=1), cardiac perforation (n=1), ventricular lead dislodgement (n=4), and device failure (n=2). Five patients suffered multiple device-related complications. Patients with pocket infection and lead failure/fracture underwent successful percutaneous mechanical lead extraction in the electrophysiology room with surgical backup in the absence of any complications. All these patients required a new lead and device replacement during the same procedure or after adequate intravenous antibiotic treatment in case of infection. All 4 ventricular lead dislodgments had an active fixation mechanism; 2 were successfully repositioned percutaneously and 2 were replaced by a new ventricular lead. Non-septic pocket

decubitus was treated with local skin excision and pocket replacement without device removal. Owing to the recurrence of decubitus, surgical pocket revision was repeated twice in one patient.

Table 9. Characteristics of patients with and without adverse ICD-related events.

	Adverse events N=26 (27.1%)	**No adverse events N=70 (72.9%)**
Age (yrs)	30 (22-34)	26 (19-30)
Sex (male)	19 (73.1)	49 (70)
Underweight status	3 (11.5)	4 (5.7)
Primary prevention	18 (69.2)	51 (72.9)
Structural cardiomyopathy	19 (73.1)	52 (74.3)
Family history of SCD	8 (30.8)	27 (38.6)
Previous syncope	8 (30.8)	32 (45.7)
Previous NSVT	13 (50)	25 (35.7)
Inducibility at PVS	3/8 (37)	16/22 (72)
Previous cardiac arrest	4 (15.4)	13 (18.6)
Previous SVT	4 (15.4)	7 (10)
Antiarrhythmic drug therapy	19 (73.1)	57 (81.1)
Minimal therapy threshold	200 (188-220)	200 (200-220)
Active fixation	15 (57.7)	43 (61.4)
Single coil	4 (15.4)	28 (40)
Single chamber ICD	23 (88.5)	60 (85.7)

* *Only for patients affected by ARVC, DCM, HCM and LVNC*

** *Only for patients affected by HCM*

Categorical variables are presented as number of patients (%). Continuous values are expressed as median with 25% and 75%-iles.

Abbreviations as in Table 7. (HR=heart rate; ICD=implantable cardioverter defibrillator)

The patient with cardiac perforation was transferred to the operating room where the lead was removed and a new lead was reimplanted via left subclavian vein in the absence of any complications. Three patients who developed device-related

complication requiring surgical revision (nonseptic pocket decubitus n=2 and lead failure n 1=1) received a subcutaneous ICD (S-ICD) after lead extraction. No patients died because of ventricular arrhythmias or device-related complications requiring surgical revision.

Predictors of inappropriate events and device-related complications

Univariate and multivariate analysis for predictors of inappropriate ICD interventions and device-related complications requiring surgical revision are listed in Tables 10 and 11. At univariate analysis, a threshold for ICD therapy less than 300 ms was associated with a borderline significant lower probability of inappropriate ICD interventions (HR=0.2; 95% CI 0.02-1.2; p=0.07).

Table 10. Predictors of inappropriate ICD interventions during follow-up.

	Univariate analysis		
	HR	**CI**	**P**
Age (years)	1.06	0.9-1.2	0.233
Sex (male)	1.45	0.3-7.0	0.641
Primary prevention	0.50	0.1-1.9	0.299
Structural cardiomyopathy	1.50	0.3-7.3	0.614
Single lead ICD	1.47	0.2-11.9	0.718
Apical position	0.62	0.1-5.1	0.653
Double coil	2.64	0.3-21.9	0.368
Active fixation	1.35	0.3-5.7	0.680
Minimum HR threshold <300 ms	0.20	0.02-1.2	0.07
Antiarrhythmic drug therapy	1.33	0.3-6.4	0.723

HR=heart rate; ICD=implantable cardioverter defibrillator.

At univariate analysis, underweight status and age at the time of implant were significantly associated with the risk of device-related complications, whereas at

multivariate analysis only underweight status remained significant (HR=5.4, 95% C.I. 1.5-19.4; p=0.01).

Table 11. Predictors of device-related complications during follow-up.

	Univariate analysis			Multivariable analysis		
	HR	**CI**	**P**	**HR**	**CI**	**P**
Age (years)	1.07	1.0-1.2	0.051	1.08	0.91-1.16	0.32
Sex (male)	0.66	0.3-1.7	0,374			
Primary prevention	1.99	0.7-6.0	0.219			
Structural cardiomyopathy	1.35	0.5-3.8	0.560			
Underweight status	3.86	1.1-13.4	0.034	5.43	1.5-19.4	0.01
Single lead ICD	1.83	0.4-7.9	0.417			
Apical position	1.02	0.1-7.9	0.983			
Double coil	1.14	0.3-4.3	0.843			
Active fixation lead	2.63	0.9-7.6	0.072			
Previous cardiac arrest	1.24	0.4-3.7	0,697			
Antiarrhythmic drug therapy	0.87	0.3-2.3	0.770			

ICD=implantable cardioverter defibrillator.

Third study: prevalence of Brugada syndrome in Kennedy's Disease

Patients' ages ranged from 27 to 78 years (mean 57.3 years; standard deviation of 10.2). The mean disease duration since disease onset, which occurred on average at 42.26±9.4 years (range 29–64; median=46), was 13.1±6.9 years (range 0–29; median=13). Twenty-seven patients had hypertension and three had ischaemic heart disease. There was no evidence of specific structural heart muscle disease. Three patients (4%) had Brugada-like ECG changes. One patient showed a type 2 'saddleback' pattern in the standard V1-V2 precordial leads (fourth intercostal space), which became type 1 'coved type' in upward right precordial leads (third intercostal space); in the other two patients, Brugada ECG changes were detected only in the right precordial leads placed in the third intercostal space and both were non-diagnostic 'saddleback' patterns (types 2 and 3, respectively). Other ECG alterations were identified in 15 (20.5%) patients, mostly consisting of left ventricular hypertrophy, pathological Q-waves (4 cases) and intraventricular conduction abnormalities (3 cases).

DISCUSSION

The two present prospective studies bring new insights in the risk stratification and therapy of patients affected by BS and other cardiomyopathies or channelopathies. The first study was designed to assess the clinical determinants of arrhythmic outcome in patients with an ECG diagnostic for BS (spontaneous or drug induced) during a long-term follow-up, with particular reference to evaluation of the prognostic value of ECG abnormalities. The mayor study finding was that the presence of first-degree AV block on basal ECG was an independent predictor of malignant arrhythmic events in addition to a traditionally recognized risk factor, i.e. a spontaneous “coved-type” ECG pattern.

The second prospective study was designed to assess the balance between the efficacy in preventing SCD and the risk of complications of ICD therapy in young individuals with primary cardiomyopathies and channelopathies during a long-term follow-up. Our principal result was a considerable high incidence of ICD related adverse events (annual rate of first ICD-related adverse event of 5.4%/year); this result highlights the need of an accurate evaluation of risk/benefit ratio of ICD implantation in this age group of patients.

Finally, we conducted a third study, analysing 73 ECGs of patients with KD with the purpose to confirm or exclude the presence of a Brugada phenotype. We found a lower incidence of Brugada ECG pattern than that reported in the Japanese study (117) and no patients presented with ventricular arrhythmia or SCD; however, 4% of our Italian population with KD had Brugada like ECG-changes. Our results revealed the need for an accurate and serial ECG evaluation to identify Brugada-like abnormalities in patients with KD.

Risk stratification in Brugada syndrome

Risk stratification is of great importance in the clinical management of patients with BS, because it allows the identification of patients with a high probability of a malignant arrhythmic outcome and eligible for ICD implantation. The low prevalence of the disease and the low incidence of arrhythmic fatal events during follow-up make risk stratification a clinical challenge, particularly in patients with no history of previous cardiac arrest. The present prospective study on a large cohort of BS patients from the Veneto region of northeastern Italy found that a history of cardiac arrest or syncope was a strong predictor of future arrhythmic events. Furthermore, we demonstrated that among ECG parameters, the presence of first-degree AV block was an independent and powerful predictor of VF/SCD in patients displaying a coved-type ST-segment elevation diagnostic for BS, either spontaneous or drug-induced.

Clinical variable and risk stratification

Previous studies demonstrated that cardiac arrest is a strong indication for ICD implantation in BS patients because of the high recurrences of malignant arrhythmic events during long-term follow-up (93-95, 106, 111). Also syncope is a strong marker of high arrhythmic risk, particularly when occurs in the absence of prodromes and specific triggering circumstances; different studies found syncope an independent predictor of malignant arrhythmic events in patients with BS, underling the need of a prophylactic ICD in those cases (93, 95, 97, 106). Our results are in agreement with those from the previous studies and underlie the prognostic value of symptoms in BS (Table 12); history of syncope and/or cardiac arrest was an independent predictor of major arrhythmic events during long-term follow-up. In literature, the incidence of major arrhythmic events in patients with history of syncope was lower compered with patients presenting after aborted SCD; moreover, the studies from

Priori *et al.* found syncope as an independent predictors od arrhythmic events during follow-up only in combination with the presence of a spontaneous type I ECG (98, 112). This is probably due to the different pathogenic mechanism underling syncopal episodes in BS. Syncope can be the clinical manifestation of a self-terminating ventricular arrhythmia or can be of vaso-vagal origin; the latter one is a benign clinical manifestation and patients presenting with a vaso-vagal syncope have usually a good prognosis. This hypothesis may explain the contrasting results of Conte *et al.*, where syncope was not a predictor of arrhythmic events during follow-up (94). All this data shown that in the clinical practice it could be challenging to distinguish this two types of mechanisms underling syncope; nevertheless, patients with syncopal episodes should be considered as a high-risk group, particularly in combination with other markers of increased arrhythmic risk.

We confirmed the poor prognostic role of family history (93, 95, 97, 106, 113) both of BS and of SCD in predicting malignant arrhythmic events during follow-up. This probably reflects the complex genetic backgrounds of the BS; the phenotypic expression of the disease is probably the results of the effects of multiple gene mutations and also environmental factors play an important role.

Electrophysiological study and risk stratification

Controversial results emerged from different studies about the prognostic role of EPS with PVS. The studies from Brugada (Table 12) brothers highlighted the prognostic role of inducibility at EPS (94, 99, 113, 114); on the contrary, data from other groups were not able to find a significant association between EPS study results and the arrhythmic outcome (93, 98, 106, 112).

In agreement with the latter studies, in our analysis inducibility at PVS is not a predictor of events during follow-up.

ECG abnormalities and risk stratification

Previous studies reported the important role of ECG in risk stratification in BS, depolarization and repolarization abnormalities being predictors of malignant arrhythmic events during follow-up.

Table 12: Clinical and electrophysiological variable associate with an increased risk of mayor arrhythmic events during follow-up.

Clinical Variable	No. pts	Study design	Prevention	Study endpoint	Multivariable analysis [hazard ratio (95% confidence interval), P value]	References
Cardiac Arrest	176	Single center; prospective	P/S	Appropriate ICD shock	5.13 (2.03 - 12.96); p<0.01	Conte 2015
	246	Single center; prospective	P/S	Appropriate ICD shock, death	19.61 (4.12 - 90.91) p < 0.001	Tokioka 2014
	308	Multicentre; prospective	P/S	Appropriate ICD therapy	10.15 (4.4 – 23.6)	Sacher 2013
	1029	Multicentre; prospective	P/S	SCD, appropriate ICD shock, sustained VT/VF	11 (4.8 - 24.3); p<0.001	Probst 2010
Syncope	246	Single center; prospective	P/S	Appropriate ICD shock, death	28.57 (6.14 - 142.86) p < 0.001	Tokioka 2014
	308	Multicentre; prospective	P/S	Appropriate ICD therapy	2.5 (1.2 – 5.2)	Sacher 2013
	320	Multicentre; prospective	P	SCD; VT/VF on stored ICD electrograms		Delise 2011
	1029	Multicentre; prospective	P/S	SCD, appropriate ICD shock, sustained VT/VF	3.4 (1.6- 7.4); p=0.002	Probst 2010
Syncope and spontaneous type I ECG	308	Multicentre; prospective	P	VF; appropriate ICD interventions	4.20 (1.38 - 12.79) p= 0.012	Priori 2012
Inducibility on EPS	176	Single center; prospective	P/S	Appropriate shock	3.38 (1.33 - 8.59) p = 0.01	Conte 2015
	547	Single center; prospective	P	SCD, VF	5.88 (2.0 – 16.7) p = 0.0001	Brugada 2003
VRP < 200 ms	308	Multicentre; prospective	P	VF; appropriate ICD interventions	HR: 3.91 (95% CI: 1.03 to 12.79, p 0.045)	Priori 2012

Abbreviations: P=primary; S=secondary; SCD=sudden cardiac death; VF=ventricular fibrillation; VRP=ventricular refractory period; VT=ventricular tachycardia.

Among repolarisation abnormalities, the presence of a spontaneous type I Brugada ECG pattern on basal ECG was found in different studies to be one of the strongest predictors of a poor arrhythmic outcome (93, 97, 98, 112); our results are in agreement with those previous studies, as a spontaneous type I ECG was at the multivariate analysis an independent predictors of events.

Other repolarisation abnormalities, like QT prolongation (107) and early repolarisation in the infero-lateral leads (106, 108-110), have been associated with arrhythmic events during follow-up, but our data did not confirm this association.

Depolarization abnormalities are frequently present in the basal ECG of Brugada patients; their prognostic role has also been evaluated in different studies but remains elusive and none of ECG conduction parameters are currently used in the risk stratification algorithms. In a retrospective analysis of 325 ECG of patients with BS, Maury *et al.* documented a first degree AV block (PR≥200 ms) in 35% of cases and found that it was independently associated with either SCD or appropriated ICD discharges (101). Another retrospective study showed that a longer PR interval was associated with SCD in women (66). Kanda et al. found longer HV intervals and broader QRS in patients with BS who were inducible to VF at PVS compared with non-inducible patients, although such conduction abnormalities did not predict the arrhythmic outcome (115). Finally, a wider QRS complex in the precordial leads was found to be a significant and sometimes independent predictor of life-threatening ventricular arrhythmias in BS (102, 103). The only depolarization abnormalities associated with a malignant arrhythmic outcome in different prospective studies were the presence of fragmented QRS at basal ECG (98, 106) and of a S-wave in lead I (105).

The present investigation differs from these prior retrospective analyses with regard to the prospective study design. In our large cohort of BS patients from the Veneto region of Northeastern Italy, we found that 16.5% of cases showed a first-degree AV block on their basal 12-lead ECG. Of interest, first-degree AV block was shown to be

the result of an infra-hissian conduction delay in 78% of the subgroup of patients (24 of 27) who underwent EPS with intracardiac AV conduction time measurements. Compared to BS patients with a normal PR interval, those with first-degree AV block also showed a wider QRS.

Our data, confirm and extend the observations of previous retrospective studies on the association between conduction disturbances and poor outcome in Brugada syndrome by demonstrating that the presence of first degree AV block (PR interval ≥200 ms) is an independent and powerful predictor of VF/SCD in patients displaying a "coved-type" ST-segment elevation diagnostic for Brugada syndrome, either spontaneous or drug-induced.

In our cohort of BS patients, we did not find any significant association between the presence of an S wave in lead I or of a fragmented QRS at basal ECG and arrhythmic outcome, either by univariate and multivariable model.

Overlapping phenotype of Brugada syndrome and cardiac conduction disease

BS is an inherited disease caused by mutations in 18 different genes, the *SCN5A* gene being the most commonly involved gene (70). The *SCN5A* gene encodes the predominant *α*-subunit of the sodium channel protein $Na_v1.5$ and its mutations in BS are responsible for a reduction in the fast inward sodium current (I_{na}). However, only 11–28% of total BS probands carry a mutated SCN5A-gene; less frequent mutations associated with BS involved genes that influence with different pathways the same cardiac sodium current I_{na} or, alternatively, the basal inward *L*-type calcium current or the transient outward potassium current I_{to} (70). The sodium current I_{na} plays a crucial role in the development of the depolarising phase 0 of the AP, and so it is a mayor determinant of excitability of myocardial cells and of impulse conduction velocity through the heart; an impairment of the current balance of the AP and of cardiac conduction is expected to occur in a subset of BS patients (80).

Different mutations in the *SCN5A* gene account not only for BS but for a variety of clinical phenotypes, also called "*sodium ion-channelopathies*" (128). SCN5A-mutations have been associated with BS, long QT syndrome type 3, sick sinus syndrome, atrial still stand, progressive cardiac conduction diseases (Lenègre disease), and possibly dilated cardiomyopathy (128). Originally these different inherited arrhythmic syndromes were considered as separate clinical entities; in contrast, recent data suggested that SCN5A-mutation carriers tend to exhibit overlapping clinical manifestations of the distinct SCN5A-related syndromes, which is defined as 'SCN5A overlap syndrome'. It has been postulated that there is an overlap between Lenègre disease and BS. Lenègre disease is associated with a genetically defective *SCN5A*-gene, like BS; it is a progressive disease of the specialized conduction tissue characterized by fibrofatty atrophy of the His-Purkinje system. Clinical manifestations of progressive cardiac conduction disease are characterized by prolongation of PR/HV intervals and widening of QRS complex with a bundle branch block, fascicular block or both, which reflect a reduced excitability and conduction delay of the His-Purkinje system as a consequence of genetically defective cardiac sodium channel (129, 130).

It has been already demonstrated that the same mutation in the *SCN5A* gene can lead either to BS or to an isolated cardiac conduction defect in the same family; the mechanism of this different phenotypic expression of the same genetic defects is not well elucidated, although some studies suggested that the existence of modifiers genes play an important role. In this regard, data of experimental studies suggest that the presence of a prominent I_{to} may determine whether loss-of-function mutations resulting in a reduction in I_{na} will manifest as a BS or a conduction disease (70, 128).

The results of the present and some previous studies confirmed that patients with BS might exhibit variable degree of conduction abnormalities such as prolonged PR/HV intervals and widening of QRS complex with right bundle branch block

morphology (101, 102, 104). This has been recognized since the initial reports on the ECG features of Brugada syndrome, when Corrado *et al.* found a coexistent conduction disturbance in 4 of 19 SCD victims with a Brugada-like right precordial ST segment elevation (104). Hence, an attractive hypothesis is that these finding can be interpreted as expression of variable degree of overlapping phenotypes -BS and Lenegre disease- due to a common genetically determined reduction of I_{na}. Moreover, we found that the presence of a conduction disturbance (first degree AV block) was an independent predictors of events in patients exhibiting a diagnostic Brugada ECG, suggesting a worse arrhythmic outcome in patients presenting with an overlapping phenotype. The explanation of the adverse outcome of patients with a phenotype that combines features of BS and conduction disease remains speculative. A possible hypothesis is that BS and Lenègre conduction disease are both manifestations of the spectrum of phenotypes related to I_{Na} reduction, and may present in isolation or in combination. The coexistence of some degree of AV conduction slowing in patients with a diagnostic Brugada ECG may be a reflection of a more complex and severe phenotype, which in turn may account for a more malignant arrhythmic outcome by a "dose effect" mechanism.

ICD therapy in young patients with cardiomyopathies and channelopathies

The major findings of our second study were the following: first, ICD therapy provided life-saving protection by effectively terminating all life-threatening ventricular arrhythmias; second, the annual rate of first appropriate ICD intervention was 4%/year, whereas the annual rate of first ICD-related adverse event was 5.4%/year, suggesting that the balance between the potential benefit and risk of complications of ICD implantation should be taken into particular account in this age group; third, underweight status was the only independent predictor of

device-related complications requiring surgical intervention, whereas there was a borderline significant association between ICD therapy threshold and inappropriate ICD interventions; and fourth, lead failure/fracture was the most common complication occur- ring in nine (9.4%) patients, highlighting the need for potential alternative ICD implantation techniques.

ICD therapy is increasingly being used in young adults for prevention of SCD in the setting of a heterogeneous group of diseases, including structural cardiomyopathies and cardiac channelopathies (15, 29, 31, 41, 42, 46, 57, 94, 70). Previous studies, largely in adult patients, have uniformly demonstrated that ICD therapy is a 'life-saving' strategy in patients with inherited cardiac diseases with prior spontaneous VT or VF, because of their high incidence of ventricular arrhythmias recurrence (29, 41, 57, 93-95). In young patients with primary cardiomyopathy and no prior spontaneous life-threatening ventricular arrhythmias, prophylactic indications for ICD implantation are still a matter of debate because the probability of arrhythmic cardiac arrest may not be sufficiently high to justify ICD therapy. Moreover, young ICD recipients with inherited cardiac diseases have a higher life expectancy and a more active life than the general population of adults with ICD, and this might result in a higher burden of device complications, including lead malfunction and inappropriate shocks, leading to surgical revision and reduced quality of life (31, 46, 56, 94, 118, 119, 126). As a result, the risk – benefit ratio of ICD in young cardiomyopathy patients should be considered carefully.

An important finding of our study is that 20.8% of patients experienced at least one appropriate intervention, and 9.4% experienced at least one intervention to terminate VF/ventricular flutter, an arrhythmia that is likely to be fatal if left untreated. However, the incidence of complications, including inappropriate shocks and device-related complications, was also high (27.1%).

According to our findings, inappropriate shocks remain a common problem, occurring in 9.4% of patients, a figure that is lower than that reported by other

studies focusing on young patients with inherited arrhythmia syndromes (range 14–28%) (29, 31, 46, 56, 93, 94, 118, 119, 132). This lower incidence compared with previous study results may be explained by the different age of patient populations and the different ICD characteristics and programming. In the present study, both patients' characteristics (such as use of antiarrhythmic drug therapy) and ICD characteristics (particularly single-chamber versus dual-chamber ICD) were not associated with an increased risk of inappropriate ICD therapies. These findings were supported by others (31, 119, 132, 133). Thus, single-chamber ICD appears to be the most appropriate option for young high-risk patients with cardiomyopathy, given the lower potential for lead complications than is expected with dual-chamber devices. Instead, a minimum threshold for intervention higher than 300 ms was a borderline significant predictor of inappropriate ICD interventions, supporting previous studies demonstrating that high threshold and long detection programming are associated with reductions in inappropriate therapy and all-cause mortality during a long-term follow-up (120, 134, 135). In our study, only one therapy zone was programmed in the majority of patients (57.3%), and the median threshold for intervention was 300ms. This programming may contribute to reducing the risk of inappropriate interventions. The incidence rate of adverse ICD-related complications in our prospective study was similar to that reported in other investigations (3.3–9.5%/year). Olde Nordkamp *et al.* in a single-centre retrospective study focused on patients with inherited cardiac disease and reported an overall incidence rate of any complication of 7.1%/year (119). At variance with this study, we focused on post-implantation ICD complications only, excluding from the analysis acute complications (i.e. pneumothorax, haemothorax and acute cardiac perforation during procedure), and this may explain the lower incidence of ICD complications in our study cohort compared with that reported by Olde Nordkamp *et al*.

Our study results demonstrated that baseline clinical characteristics such as underweight status at the time of implantation, but not ICD lead characteristics, were predictors of adverse device-related events. Among all complications, lead failure/fracture requiring lead extraction was the most common adverse event. Our findings confirm previous studies in both the young and adult ICD populations, reporting that the lead system constitutes the 'weakest link' in the ICD system and may not be designed to remain intact and perform effectively over the long periods required for young patients with decades of productive life ahead (119, 126, 127). Remote monitoring is now increasingly used for early diagnosis and management of device-related complications in patients with ICD (136, 137).

A reduced ICD lead diameter may be a particularly useful feature in young patients. Thus, small-diameter ICD leads, including Sprint Fidelis and Riata leads, have been introduced into clinical practice to facilitate the implantation procedure and to potentially reduce the likelihood of venous obstruction and tricuspid valve distortion (126). However, different reports have demonstrated an increased rate of complications with small-diameter leads, raising the question of whether failure of ICD leads is a matter of lead size (138). Recently, Janson *et al.* demonstrated that design rather than diameter is the critical issue in ICD lead survival in young patients (127). In our study, among patients with leads failure, only one patient was implanted with Sprint Fidelis lead and none with Riata lead, highlighting that lead failure is a common ICD-related complication in young patients indepen- dently from lead characteristics.

Apart from lead characteristics, classical subclavian vein access as first choice, used in all our patients during the study period, may have increased the risk of lead failure. In our study, we observed two cases of 'subclavian crush syndrome', which is a common long-term lead complication following subclavian vein access, suggesting that the type of implantation technique is a critical issue to minimize the risk of lead fracture (139). In this regard, axillary vein or cephalic access for ICD lead may offer

the potential to avoid lead complications usually observed with traditional subclavian vein approach (140, 141). These techniques are currently used in all patients undergoing ICD implant in our department.

S-ICD has recently entered into the clinical practice and may represent a valid alternative to the traditional transvenous device, especially among patients with limited vascular access, increased risk of infection and structurally normal heart with no need for pacing (11, 143, 144). The lack of transvenous and intracardiac components makes it an attractive choice also for young patients. However, the precise clinical role of S-ICD in young patients with cardiomyopathy remains to be defined because of the possibility of an increased risk of T-wave oversensing and inappropriate shock delivery, especially in patients with hypertrophic or arrhythmogenic cardiomyopathy (145, 146). Moreover, the decision whether to implant a leadless device needs to be patient specific, balancing potential lead-related complications with the likelihood of recurrent VT that may be effectively pace-terminated. Although no patient died from ICD complications, adverse events increase the number of hospitalizations, surgical revisions and clearly constitute a source of incremental costs to the healthcare system as well as reducing the quality of life.

Device longevity is also a very important aspect in the clinical practice both for patients' safety, because device replacement carries a potential risk of serious complications including pocket infection, and for healthcare systems, because of the high costs of ICD. The impact of extending ICD longevity is particularly important in young individuals with preserved left ventricle systolic function, a subset of patients with a relatively long survival in whom avoidance of device replacements is paramount (147, 148).

Kennedy's Disease

In our analysis, there was no sign of a structural cardiomyopathy in our patients, as previously described (149). A recent study reported a high prevalence (11.8%) of Brugada-like ECG in a Japanese population with KD, ascribed to a down regulation of the SCN5A gene leading to sodium current reduction in the myocardium (117). Of note, two patients had symptomatic Brugada syndrome and died suddenly during follow-up. In our study, we found non-diagnostic Brugada ECG abnormalities in three patients (4%), mostly recorded in non-conventional upward right precordial leads (third intercostal space), and not associated with any relevant symptom. This prevalence is significantly lower than that reported in the Japanese study: the discrepancy may be explained by the different ethnic background, the Brugada syndrome being more frequent in the Asian than the Caucasian population. Although no SCD events were observed in our cohort, our findings confirm the need for accurate and serial ECG evaluation to identify Brugada-like repolarisation abnormalities. Thus, our suggestion is to record lead V1-V2 over the III and II intercostal space, to enhance the sensitivity for detection of Brugada like ECG-changes. Patients presenting with a Brugada-like ECG should be prudently advised to prevent and correct hypokalaemia, to promptly treat a fever >38° by antipyretic therapy, and to use caution in taking antiarrhythmic drugs known to worsen ECG abnormalities and potentially trigger ventricular tachyarrhythmias in BS.

CONCLUSIONS

The present studies provide new insights in the risk stratification and treatment of patients with cardiomyopathies and channelopathies.

The first study indicates that besides a history of cardiac arrest or syncope, first-degree AV block is an independent predictor of malignant arrhythmic events and a stronger marker of arrhythmic risk than a spontaneous “coved-type” ECG pattern. The coexistence of “coved-type” right precordial ST-segment elevation and prolongation of PR interval in those BS patients showing a higher risk of VF supports the concept of a “sodium ion channelopathy” whose increased myocardial electrical instability is the result of a complex interaction between myocardial repolarization and depolarization abnormalities. Further experimental and clinical studies are needed to better characterize the genetic background, the arrhythmogenic mechanisms, the risk stratification accuracy and the therapeutic implications of such a dual sodium channel-related phenotype. At the moment, this easily available ECG marker should be considered among the clinical and instrumental parameters used in designing clinical algorithm for individual risk assessment in BS.

Our second study reinforces the concept that in young patients with primary cardiomyopathies and channelopathies ICD therapy provides life-saving protection by effectively terminating life-threatening ventricular arrhythmias and substantially reduced the estimated cardiovascular mortality. However, because ICD-related adverse events are common, especially lead failure requiring lead extraction, the risk/benefit ratio should be carefully assessed when considering ICD implantation in young people, especially for primary prevention. Our findings also underline the importance of preventing device-related complications with appropriate implantation techniques and programming to maintain a favourable benefit–risk balance of ICD therapy.

Finally, our third study does not confirm the high prevalence of Brugada ECG pattern in patients with KD as previously reported in a Japanese study. ECG recording with right precordial leads in the upper intercostal spaces is warranted, in order to increase the sensitivity for detection of Brugada-like ECG changes in these patients, which is a prerequisite for lifestyle changes recommendations.

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