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How to prevent sudden death in patients with inherited arrhythmia syndromes or cardiomyopathies

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Inherited arrhythmogenic myocardial diseases are distinctively characterized by the genetically determined increased risk of ventricular fibrillation and sudden arrhythmic death, predominantly in young people.[1] They include either genetic heart muscle diseases manifesting clinically with ventricular arrhythmias related to structural ventricular abnormalities (ie, hypertrophic, dilated, and arrhythmogenic right ventricular cardiomyopathy [ARVC]), or channelopathies presenting as a primarily electrical myocardial dysfunction (ie, genetic defects on cardiac ion channels, including long and short QT syndromes, Brugada syndrome, Lenegre disease, and catecholaminergic polymorphic ventricular tachycardia). Common clinical manifestations include syncopal episodes and cardiac arrest precipitated by ventricular fibrillation. Studies on genotype-phenotype correlations led to identification of health gene carriers in every condition. Programmed ventricular stimulation, which has been designed to reproduce scar-related reentrant ventricular tachycardia in postmyocardial infarction patients, is scarcely useful in a patients with inherited arrhythmogenic diseases, with or without structural abnormalities, and risk stratification mostly relies on the severity of spontaneous clinical presentation. An implantable cardioverter defibrillator (ICD) is the definitive lifesaving therapeutic option in most affected patients, whereas β-blockers may have a limited role for the management of adrenergic-dependent arrhythmias. The recent development of molecular genetics, with the discovery of a genetic role in these myocardial disorders of previously unknown origin, raised the need for a new classification that goes beyond the phenotype.[2] Accordingly, in the new definition/classification proposed by the American Heart Association,[3] all these genetically determined diseases, either structural or primarily electrical, sharing the high risk of arrhythmic sudden death, are included among the listing of inherited cardiomyopathies, regardless of their phenotype.

The session focused on arrhythmia mechanisms and prevention of sudden death in patients with arrhythmogenic genetic cardiomyopathies.

Changes in electrical properties of the myocardium in the early stage of ventricular hypertrophy—L. Bacharova

Dr Bacharova examined the changes in electrical properties of the myocardium in the early stage of ventricular hypertrophy.

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Electrophysiological remodeling is a term comprising complex changes in electrical properties of the myocardium, creating conditions for triggering and maintaining of arrhythmias.[4] Arrhythmias are the late manifestations of cardiac pathology; however, the process of remodeling already starts in its early stages. The question arises as to whether and how remodeling is manifested in the electrocardiogram (ECG) long before arrhythmias occur. The identification of such early changes in the ECG would be of utmost diagnostic and prognostic importance in the prevention of sudden cardiac death (SCD).

In left ventricular hypertrophy (LVH), the focus is classically on the increased QRS voltage, which is recognized as a risk factor for cardiac morbidity and mortality. However, the increased QRS voltage is seen in only a small proportion of patients with increased left ventricular mass. In our previous articles, we demonstrated a novel approach to false-negative ECG results in LVH and formulated a hypothesis that these false-negative results might reflect the changes in the electrical properties of the myocardium in the early stage of LVH development.[5] The aim of this contribution was to present the hypothesis on the relative voltage deficit and provide a brief overview of changes in electrical properties of the myocardium in LVH with the focus on the depolarization changes in the early stage of LVH.

The hypothesis on the relative voltage deficit assumes that (1) a unit of pathologically changed myocardium in LVH is a less efficient generator of cardioelectric field as compared with a unit of healthy myocardium, (2) the relative voltage deficit already starts in the early stage of LVH development and varies with its progress, and (3) the relative voltage deficit is caused by altered electrical properties of the myocardium due to electrophysiological and structural remodeling. The specific potential of the myocardium, calculated as the ratio of the QRS voltage and left ventricular mass, has been introduced as a measure for the relative voltage deficit. Clinical and experimental evidence support the hypothesis on the relative voltage deficit.[6-8] Determinants of electrical impulse propagation possibly explaining the discrepancies between ECG and echocardiographic findings in LVH in hypertension are extensively studied in relation to electrophysiological remodeling in arrhythmias[4,9-11] and provide a basis for explanation of the relative voltage deficit in the early stages of LVH.

Arrhythmogenic right ventricular cardiomyopathy: antiarrhythmic drugs, catheter ablation, or implantable cardioverter defibrillator?—D. Corrado

Dr Corrado discussed the management strategy for prevention of SCD in patients with ARVC, with particular reference to ICD therapy.

Arrhythmogenic right ventricular cardiomyopathy is an inherited heart muscle disease that is characterized pathologically by fibrofatty replacement of the right ventricular myocardium and clinically by peculiar electrical instability leading to ventricular tachycardia or ventricular fibrillation, which may precipitate SCD mostly in adolescents and young adults.[12-14] Later in the natural history, heart failure may occur as the result of progression of right ventricular disease and left ventricular involvement.[12] The first objective of management strategy is to prevent arrhythmic cardiac arrest. However, there are no prospective and controlled studies assessing clinical markers that can predict the occurrence of life-threatening ventricular arrhythmias. Because the risk stratification of sudden death in patients with ARVC is still not well established, there are no precise guidelines to determine which patients need to be treated and which is the best management approach.[14] The risk profile that emerges from retrospective analysis of clinical and pathologic series, including fatal cases, is characterized by youthful age, competitive sport activity, malignant familial background, extensive right ventricular disease with ejection fraction reduction and left ventricular involvement, episodes of complex ventricular arrhythmias or ventricular tachycardia, syncope, and previous cardiac arrest.[12, 13] At present, the main therapeutic options include antiarrhythmic drugs, catheter ablation,

and ICD.[14,15] Pharmacologic therapy is the first-choice treatment of patients with well-tolerated and non–life-threatening ventricular arrhythmias. The evidence available suggests that either sotalol or amiodarone (alone or in combination with β-blockers) is the most effective drug with a relatively low proarrhythmic risk. Nonpharmacologic therapy is reserved for drug-resistant cases and for patients with previous arrhythmic cardiac arrest. Catheter ablation of the ventricular tachycardia reentry circuit has acute success rates of 60% to 90%. However, ventricular tachycardia relapses are frequent (up to 60% of the cases) and have been attributed to development of new arrhythmogenic zones because of the progressive nature of the underlying disease.

The implantable defibrillator has become the treatment of choice for prevention of sudden death in patients with ARVC.[15] Indications for ICD implantation in patients with ARVC in the past were largely empiric and based widely on the experience gained by different centers using analogies with other conditions requiring antiarrhythmic therapy. Moreover, there was a growing tendency to implant ICD indiscriminately once the disease had been diagnosed regardless of risk stratification. The "Darvin study"[15] was the first observational study to address the efficacy and safety of ICD therapy in a relatively large population of patients with ARVC treated for both secondary and primary prevention of SCD. The study reported that during a mean 3.3-year follow-up, approximately 50% of the 132 patients had at least one appropriate ICD intervention despite antiarrhytmic therapy. Furthermore, 24% of the total patient population experienced one or more episodes of ventricular fibrillation/flutter that in all likelihood would have been lethal in the absence of the device therapy. Analysis of risk factors showed that younger age, a history of cardiac arrest or hemodynamically unstable ventricular tachycardia, left ventricular involvement and syncope were independent clinical variables associated with the occurrence of such life-threatening arrhythmias. Of interest, therapy with ICD did not improve survival in the subgroup of patients presenting with hemodynamically stable monomorphic ventricular tachycardia and treated with antiarrhythmic therapy. Finally, ICD therapy was substantially safe as shown by the relatively low rate of either inappropriate interventions or ICD-related complications. With regard to arrhythmic risk stratification, electrophysiological study was of limited value in identifying patients prone to ventricular fibrillation/flutter and candidates for ICD implantation. Programmed ventricular stimulation showed a low predictive accuracy for subsequent appropriate ICD intervention, with approximately 50% of both false-positive and false-negative results. These findings are in keeping with the limited predictive value of electrophysiological study in conditions other than ischemic heart disease, such as hypertrophic and dilated cardiomyopathy. Thus, patients with ARVC who need an ICD because of a high risk of arrhythmic SCD are better identified on the basis of their clinical presentation.

The available evidence indicates that in patients with familial ARVC genotyping is not able to predict phenotype or prognosis on the basis of characterization of malignant vs benign mutations.[16]

The Brugada syndrome: who is at risk? What are the markers?—C. Antzelevitch

Dr Antzelevitch discussed the risk stratification for arrhythmic sudden death in patients with Brugada syndrome.

The Brugada syndrome (BS) is characterized by an ST-segment elevation in the right precordial ECG leads.[17-19] Death commonly occurs during sleep secondary to ventricular tachycardia or fibrillation, which is often precipitated by a closely coupled extrasystole. This disorder is inherited with an autosomal dominant mode of transmission. BS phenotype is much more prevalent in men than in women (75%-90% men) due at least in part to differences in the

transient outward current (I_{to}). The syndrome is most prevalent in Southeast Asia, with an incidence of 5 in 10000. The BS ECG is often concealed but can be unmasked by potent sodium channel blockers. Recent experimental studies indicate that the combination of sodium and calcium channel block may be more effective.[20] Four cases of BS have been linked to mutations in SCN5A, the α subunit of the sodium channel, in approximately 20% of cases. Mutations in glycerol-3-phosphate dehydrogenase 1-like (GPD1L) gene have recently been identified as another cause.[21] In a preliminary report, a mutation in GPD1L was shown to result in a partial reduction of I_{Na}. Three types of SCN5A mutations have been identified in the BS: splice donor, frameshift, and missense, all leading to a loss of function. A marked reduction in I_{Na} is thought to cause the BS by leaving I_{to} unopposed. This leads to an accentuation of the action potential notch, particularly in the right ventricular epicardium where I_{to} is most prominent, eventually leading to loss of the action potential dome and marked abbreviation of action potential duration. Loss of the action potential dome in the epicardium but not endocardium gives rise to a large dispersion of repolarization across the ventricular wall, resulting in a transmural voltage gradient that manifests in the ECG as an ST-segment elevation (or idiopathic J wave). Under these conditions, heterogeneous repolarization of the epicardial action potential gives rise to phase 2 reentry, which provides an extrasystole capable of precipitating ventricular tachycardia/fibrillation (VT/VF).[22] Risk stratification of patients with the BS has been an issue of lively debate.[23,24] It is generally accepted that patients with BS presenting with aborted sudden death are at high risk. There is also little argument that patients presenting with syncope are at high risk, particularly when the clinical history suggests an arrhythmic syncope (as opposed to typical vasovagal syncope) and the ECG shows a type I abnormality. In contrast, risk stratification of asymptomatic patients has met with considerable debate. Several invasive and noninvasive parameters have been proposed for identification of patients at risk for sudden death, including the presence of spontaneous type 1 ST-segment elevation, the characteristics of the S wave, the presence of late potentials, and inducibility of VT/VF using programmed electrical stimulation. Whereas the Brugada brothers have advanced considerable data indicating that VT/VF inducibility can identify patients with BS at risk for SCD, several other investigative groups have failed to demonstrate a relationship. The reason behind the disparity is not clearly evident. Gehi et al[25] recently reported the results of a meta-analysis of 30 prospective studies that included 1545 patients with a Brugada ECG to assess predictors of events. The meta-analysis suggested that a history of syncope or SCD, the presence of a spontaneous type I Brugada ECG, and male sex predict a more malignant natural history. The findings, however, did not support the use of a family history of SCD, the presence of an SCN5A gene mutation, or electrophysiological study to guide the management of patients with a Brugada ECG. The results of the meta-analysis should be viewed with some reservation in that the study pooled data from prognostic studies that used very different criteria to identify patients with BS. Moreover, the 6 studies that were used to evaluate the role of electrophysiological study in risk stratification of patients were quite heterogeneous. ICD implantation is the only proven effective treatment.[26,27] The pharmacologic approach to therapy is focused on block of I_{to} or augmentation of I_{Ca}; both interventions lead to restoration of the action potential dome and the elimination of the arrhythmogenic substrate. I_{to} block by quinidine and tedisamil have been shown to be effective in preventing VT/VF in experimental models of BS, and quinidine has been shown to normalize the ST-segment elevation in some patients with BS.[28]

Long QT syndrome: how far is genotype-related risk assessment—J. Kanters

Dr Kanters discussed the current role of genotyping for risk assessment and therapy of patients with long QT syndrome (LQTS).

Treatment of patients with LQTS has not changed much in the last 30 years. β-Blocker therapy is the standard choice unless the patient has experienced a cardiac arrest, in which case an ICD should be implanted.

Genotyping has made diagnosis of LQTS easier and has been shown to be fast and cost-effective.[29] An open question is "How far is genotype-related risk assessment and therapy in LQTS?" Patients with KvLQT1 (LQT1) mutations have fewer cardiac events than patients with HERG (LQT2) and SCN5A (LQT3) mutations,[30] and patients with KvLQT1 mutations are normally very effectively treated with β-blockers. β-Blocker failure is more commonly seen in patients with HERG mutations, and more of these patients end up with an ICD. Patients with HERG mutations are very sensitive to low potassium levels, and increasing potassium with potassium supplements and spironolactone is known to shorten the corrected QT interval and could be of benefit to these patients. However, it is unknown whether potassium supplements are only ECG cosmetics or of real clinical benefit. The location of the mutation also seems to matter in patients with HERG, in contrast to patients with KvLQT1 mutations. Mutations in the pore region of the HERG channel are associated with more than twice the risk of cardiac events and about half the patients experience an aborted cardiac arrest or SCD.[31] Patients with SCN5A mutations have few events, but a higher fraction of events are cardiac arrests. β-Blockers are not very effective in this rarer genotype (5%-10% of LQTS patients), but there is no evidence or indication that β-blockers are harmful for patients with SCN5A mutations. In symptomatic patients with SCN5A mutations, ICD implantation should be considered. Blocking of the overactive sodium channel with Mexilitine shortens the QT interval, but it is unknown if it affects mortality, and it should be reserved for patients with an ICD in place. Little is known about the rare genotypes (LQT4-10). MinK (LQT5) and MiRP1 (LQT6) seem more mild and are often associated with drug-induced LQTS. Timothy syndrome (LQT8) seems to be a more severe variant of LQTS, with a mortality higher than 50% and an average age of death before 3 years of age.[32] In conclusion, β-blockers are still the first therapy in patients with LQTS, but genotyping could be used as a guide for selecting patients for ICD therapy and selection of added therapy on top of β-blockers.

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