Focus on hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy

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WHICH PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY SHOULD RECEIVE AN IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR?

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Hypertrophic cardiomyopathy is a genetic and heterogeneous disease with diverse clinical course, but with a low incidence of sudden cardiac death in the general population. Nonetheless sudden cardiac death accounts for about 50% of mortality in hypertrophic cardiomyopathy, and ventricular tachyarrhythmais are the principal mechanism of this catastrophic event. Therefore, the identification of high-risk patients who are the potential candidates for implantable cardioverter-defibrillator (ICD) therapy is the first step in the management of patients with hypertrophic cardiomyopathy. The factors that best identify such patients include survived cardiac arrest or sustained ventricular tachycardia, a family history of sudden cardiac death due to hypertrophic cardiomyopathy, left ventricular hypertrophy ≥ 30 mm, syncope, symptomatic non-sustained ventricular tachycardia, and exercise-induced hypotension in patients ≤ 40 years.

The decision to implant an ICD in patients with hypertrophic cardiomyopathy depends on the symptoms and level of risk. ICD therapy is indicated in patients for secondary prevention after sustained ventricular tachycardia or ventricular fibrillation. The ICD implantation is recommended for primary prevention of sudden cardiac death in patients with two or more risk factors in whom annual rates of sudden cardiac death are 3-6% or more. The presence of extreme left ventricular hypertrophy, or a recurrent syncope on exertion should be also considered for ICD implantation in individual young patients. At present, other single risk factors, because of its imprecision in risk stratification, cannot justify prophylactic therapy with ICD.

Introduction

The main goal of the therapy with implantable cardioverter-defibrillators (ICD) is to reduce the incidence of sudden cardiac death in patients who survived cardiac arrest due to ventricular fibrillation or hemodynamic unstable ventricular tachycardia (VT)[1], or in those who are at high risk for these arrhythmias[2]. Hypertrophic cardiomyopathy is a genetic and heterogeneous disease with diverse clinical course, but with a low risk of sudden cardiac death in the general population[3]. Since sudden cardiac death may occur in asymptomatic or mild symptomatic patients, the first step in patient management is the identification of high-risk patients who are the potential candidates for ICD therapy. Unfortunately, the most of clinical features associated with an increased risk of dying suddenly have only modest positive predictive accuracy[4], making the decision to implant an ICD in patients with hypertrophic cardiomyopathy more difficult than in patients with ischemic heart disease.

Epidemiology and mechanisms

Sudden cardiac death accounts for about 50% of the mortality in hypertrophic cardiomyopathy, but its incidence depends on the study population. Earlier hospital-based clinical investigations have reported the annual incidence of sudden cardiac death from 2 to 4% in adults, and from 4 to 6% in children and adolescents[5]. In regionally selected patient populations, the annual risk of sudden death was 0.7%[3], and hypertrophic cardiomyopathy did not significantly alter the overall life expectancy[6].

In unselected patients with hypertrophic cardiomyopathy reported by Maron at al.[3],

the risk of sudden death was not confined to young patients but extended into later phase of life and without statistically significant predilection for any age group. In this study, sudden cardiac death occurred predominantly in patients with no or mild symptoms (NYHA functional class I-II), and the most of them died suddenly during or immediately after a sedentary or mild physical activity. On the other side, hypertrophic cardiomyopathy is the most common cause of sudden death in young athletes, accounting for 36% of cases[7].

The available data suggest that ventricular tachyarrhythmias are the cause of sudden cardiac death in the majority of patients with hypertrophic cardiomyopathy. In a study of 32 patients with hypertrophic cardiomyopathy and rhythm recorded at the time of resuscitation from cardiac arrest, 31 had ventricular fibrillation and 1 patient had ventricular asystole[8].

Stored electrograms from ICD in patients with hypertrophic cardiomyopathy also show VT rapidly degenerating into ventricular fibrillation before termination of the defibrillator charging period (Fig. 1)[9,10]. Efficacy of ICD shocks in restoring sinus rhythm and immediate recovery of patients after ICD intervention[9-12] argue against catastrophic hemodynamic events preceding ventricular arrhythmias in patients with hypertrophic cardiomyopathy. These data suggest that ventricular arrhythmias in hypertrophic cardiomyopathy are more likely a primary event resulting from electrical instability of an arrhythmogenic substrate (disarray or myocardial scarring), than a secondary phenomenon triggered by myocardial ischemia, outflow obstruction, diastolic dysfunction, or supraventricular tachyarrhythmias.

Risk stratification

One of the main aims on assessing patients with hypertrophic cardiomyopathy is the identification of individual risk for sudden cardiac death. Clinical parameters currently used to assess the risk level for sudden cardiac death in hypertrophic cardiomyopathy[12] are shown in table I. Unfortunately, all of these risk factors, except ventricular fibrillation and spontaneous VT, have a low positive predictive value, because the majority of patients with one of these factors will never have sudden cardiac death. On the other hand, their negative predictive value for sudden cardiac death is very high. Therefore, a patient with none of these factors has a favorable prognosis and should be allowed to conduct a normal life.

The risk is considered to be higher when two or three of the clinical parameters are associated (Table II)[4,13]. In children and adolescents with hypertrophic cardiomyopathy, syncope on exertion is an ominous symptom, but the risk is higher when syncope occurs in individuals with a family history of sudden cardiac death due to hypertrophic cardiomyopathy[4]. A similar logic should be used in patients with hypertrophic cardiomyopathy who have non-sustained VT. In these patients, non-sustained VT is prognostically significant only when being repetitive or being associated with symptoms of impaired consciousness[14]. The use of programmed ventricular stimulation to test inducibility of ventricular arrhythmias

Table I. The strongest risk factors for sudden cardiac death in hypertrophic cardiomyopathy.

Cardiac arrest (ventricular fibrillation)
Spontaneous sustained ventricular tachycardia
Familial sudden hypertrophic cardiomyopathy-related death
Syncope (particularly if recurrent, exertional, or in the young)
Non-sustained ventricular tachycardia (frequent, repetitive, or symptomatic)
Abnormal blood pressure response with exercise (in patients ≤ 40 years of age)
Extreme left ventricular hypertrophy (maximum thickness ≥ 30 mm)

Table II. Relation of clinical risk factors to 6-year survival from sudden death in patients with hypertrophic cardiomyopathy.

No. risk factors	6-year survival from sudden death (%)
0	95 (91-99)
1	93 (87-99)
2	82 (67-96)
3	36 (0-75)

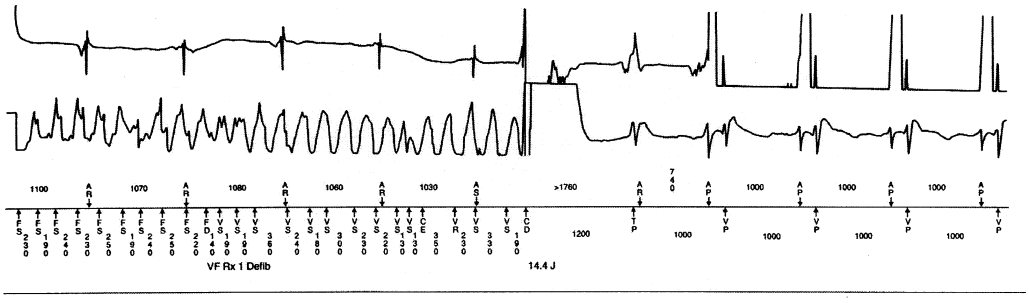

Figure 1. *Secondary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Continuous recording of stored intracardiac atrial and ventricular electrogram form a patient who had syncope, spontaneous ventricular tachycardia and extreme ventricular hypertrophy. The implantable cardioverter-defibrillator senses ventricular fibrillation and after programmed interval delivers a defibrillation shock, which restores atrioventricular pacing[10].*

in selected patients with hypertrophic cardiomyopathy is controversial[15,16]. Limitations include infrequent success of provocation of the monomorphic VT and the nonspecificity of rapid polymorphic VT and ventricular fibrillation. Although the current European guidelines for electrophysiologic procedures indicate no role for electrophysiologic studies in hypertrophic cardiomyopathy[17], we use this diagnostic procedure in patients who have non-sustained VT[18]. New possibilities in the risk stratification have been offered by finding that some gene mutation, such as cardiac troponin T and beta cardiac myosin heavy chain mutations causing hypertrophic cardiomyopathy, indicate a particularly high risk of sudden cardiac death[19]. However, the caution must be warranted before strong conclusions are derived regarding prognosis based solely on the available epidemiologic genetic data, which are relatively limited and skewed by virtue of selection bias toward high-risk families[20].

Implantable cardioverter-defibrillator therapy in secondary and primary prevention of sudden cardiac death

Earlier data on the use of ICDs in patients with hypertrophic cardiomyopathy have been limited to retrospective studies of secondary prevention in the small numbers of patients who survived cardiac arrest or had sustained VT[11,12,21,22]. At present, the two large studies are published[9,23] that provide compelling support for the use of ICD for secondary and primary prevention in selected high-risk patients with hypertrophic cardiomyopathy.

Maron et al.[9] have presented the results of a retrospective study that investigated the efficacy of ICD therapy in 128 patients with hypertrophic cardiomyopathy. The mean age of patients was 40 years. In 43 patients, ICDs were implanted for secondary prevention after either resuscitation from ventricular fibrillation, or sustained, spontaneous VT. In this group of patients, the annual rate of appropriate discharges was 11%, with a cumulative rate of 75% at 10 years. A strikingly higher rate of interventions occurred in the first 4 months after implantation, confirming that patients with hypertrophic cardiomyopathy have an unstable period. However, there were also substantial rates of recurrent and late events. In this group, the device failed to prevent death in 2 patients who had end-stage hypertrophic cardiomyopathy with severe systolic dysfunction and heart failure.

Even more important are the results in the remaining 85 patients, who received ICDs for primary prevention. The predominant clinical indications for the prophylactic implantation were syncope (n = 41), a family history of sudden death due to hypertrophic cardiomyopathy (n = 39), non-sustained VT (n = 32), and a left ventricular wall thickness ≥ 30 mm (n = 10). In addition, 61 patients had two risk factors for sudden cardiac death, and 56 had inducible VT or ventricular fibrillation during programmed ventricular stimulation. In this group of patients, the annual rate of appropriate discharges was 5%, that was significantly lower than in the secondary prevention group (Fig. 2). The cumulative discharge rate reached a plateau at approximately 20%. By extrapolating from this discharge rate, one could predict that within 10 years almost 50% of the ICDs prophylactically implanted in young patients would discharge and prevent sudden death. Relationship between appropriate ICD intervention and implant justification is shown in table III. The presence of left ventricular hypertrophy ≥ 30 mm was found as the most justified indication for primary prevention of sudden cardiac death.

The incidence of complications of ICD therapy was also significant. Inappropriate therapies were delivered in 25% of patients, due to sinus tachycardia, atrial fibrillation, or lead dislodgement, fracture, or oversensing. There was one death at the time of implantation, one hemorrhage requiring thoracotomy, and two infections requiring explantation.

Recently, Begley et al.[23] investigated the efficacy of ICD therapy in 132 patients with hypertrophic cardiomyopathy. The mean age of patients was 34 years. The indications for secondary prevention were sustained VT

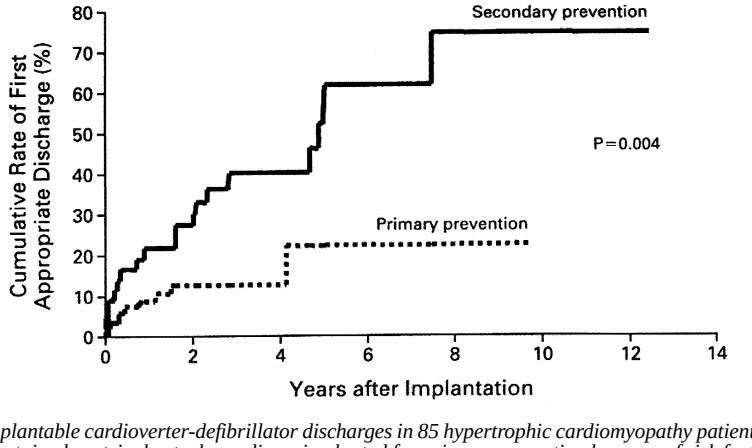

Figure 2. *Cumulative rates of implantable cardioverter-defibrillator discharges in 85 hypertrophic cardiomyopathy patients implanted for secondary prevention after cardiac arrest or sustained ventricular tachycardia or implanted for primary prevention because of risk factors for sudden cardiac death[9].*

Table III. Appropriate implantable cardioverter-defibrillator (ICD) intervention and implant justification.

Implant indications	No. patients	Appropriate ICD interventions (%)
VF or spontaneous VT	43	44
Massive LVH	10	20
Syncope	41	12
Non-sustained VT	32	6
Family history of SD	39	3

LVH = left ventricular hypertrophy; SD = sudden death; VF = ventricular fibrillation; VT = ventricular tachycardia.

or cardiac arrest in 47 patients, and the indications for primary prevention were clinical features associated with increased risk for sudden cardiac death in 85 patients. In primary prevention group, the patients had almost four risk factors for sudden death, including syncope (n = 38), non-sustained VT (n = 51), more than one sudden death in first degree relatives (n = 39), severe left ventricular hypertrophy (n = 19), abnormal blood pressure to exercise (n = 21), or inducible sustained VT (n = 46). During the mean follow-up period of 4.8 years, there were 6 deaths and 55 appropriate interventions in 27 (20%) patients. The annual therapeutic ICD intervention rate was lower in the primary prevention group than in the secondary prevention group (3 vs 7%, $p < 0.05$). However, the survival rates in the two groups were similar (94% for primary vs 98% for secondary prevention of sudden death). The cumulative intervention rate at 5 years was also significantly lower in patients in whom ICD therapy was for primary prevention than in patients who received this therapy for secondary prevention of sudden cardiac death (16 vs 26%, $p < 0.05$) (Fig. 3). None of the used risk factors was associated with significantly higher rates of therapeutic ICD interventions. Serious complications were recorded in 38 patients, including inappropriate shocks in 30 patients. The complications rates were similar for primary and for secondary prevention of sudden death.

Conclusion

The recent studies have demonstrated that ICD therapy provides life-saving protection by effectively terminating VT or ventricular fibrillation in patients with hypertrophic cardiomyopathy. Therefore, patients who have survived cardiac arrest due to ventricular fibrillation or have sustained VT without any evident precipitating cause that can be eliminated, have a class I indication for ICD therapy.

The ICD therapy is strongly recommended for primary prevention of sudden cardiac death in patients with two or more risk factors, identified during non-invasive risk stratification, in whom annual rates of sudden cardiac death are 3 to 6% or more[17]. The presence of a single risk factor is of lower positive predictive value and in most patients, decisions regarding prophylactic prevention should be individualized depending on patient age and the perceived severity of risk factors. Therefore, young patient with left ventricular thickness ≥ 30 mm[12,24], or recurrent syncope on exertion should be candidate for ICD therapy, or should be informed of potential life-saving protection offered by an ICD.

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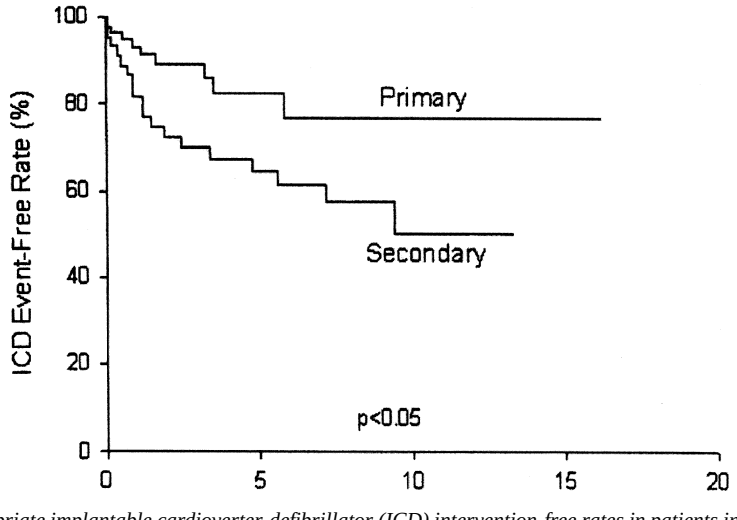

Figure 3. *Comparison of appropriate implantable cardioverter-defibrillator (ICD) intervention-free rates in patients in whom ICDs were implanted for primary and secondary prevention[23].*

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CELL JUNCTION PROTEINS ARE INVOLVED IN ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

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The most probable mechanism of arrhythmogenic right ventricular cardiomyopathy (ARVC) is the myocyte loss secondary to metabolic or ultrastructural defects. The identification of genetic mutations in desmoplakin in patients with typical dominant ARVC, with recessive ARVC and with Carvajal syndrome as well as the detection of mutations in plakoglobin in subjects with an unusual form of this disease, called Naxos disease, is consistent with this hypothesis. The paper examined the different clinical expressions associated with mutations of cell junction proteins.

Introduction

The most probable mechanism of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is the myocyte loss secondary to metabolic or ultrastructural defects.

The identification of genetic mutations in desmoplakin (DSP) and junctional plakoglobin (JUP) respectively in patients with typical dominant ARVC, in patients with recessive ARVC, in patients with Carvajal syndrome, and in subjects with an unusual form of this disease, called Naxos disease, is consistent with this hypothesis[1-4].

DSP is a constituent of the desmosomal plaque, anchoring intermediate filaments (IF) to the plasma membrane and forming a scaffold that is essential for maintaining tissue integrity.

JUP is a cytoplasmic protein and a submembranous constituent of both kinds of cell-cell adhering junctions, the desmosomal and the adherens junctions.

Arrhythmogenic right ventricular dysplasia type 8

A mutation in exon 7 of DSP was detected in all affected subjects belonging to a family with typical autosomal dominant ARVC/D. In this family, different degrees of disease involvement can be found, and subjects with affected genotype and normal phenotype can be present beside subjects with different extent of the disease and different ventricular arrhythmias.

DNA sequencing revealed a missense mutation in exon 7 (S299R). DSP, together with JUP, anchors to desmosomal cadherins, forming an ordered array of non-transmembrane proteins, which then bind to keratin IF. Desmosomes are major cell-cell junctions, particularly abundant in epidermal cells and in cardiomyocytes. DSP consists of 2871 amino acids, and it is predicted to be a homodimer containing two globular end domains joined by a central alpha-helical coiled-coil rod domain. A carboxy-terminal domain of DSP interacts with IF, whereas amino-terminal domain including 2-subdomain is required for DSP localization to the desmosomal plaque and is binding to JUP.

Mutated Ser residue in the Z subdomain represents the only PKC phosphorylation site conserved in the whole N-terminal of all proteinkinase C (PKC)-regulated plakins. Such residue is likely to represent a crucial site for PKC-mediated regulation of DSP interactions with desmosomal components at the plasma membrane side. Moreover, the first 584 amino acids of the N-terminal domain, where S299R mutation was detected, are known to be involved in JUP binding and in clustering of desmosomal cadherin-JUP complexes.

Nonsense DSP mutations, leading to functionally null alleles, were reported to producd striate palmoplantar keratoderma in heterozygotes, thus demonstrating that dosage of DSP is critical in maintaining epidermal integrity.

Conversely, heterozygotes for DSP truncated at its C-terminal domain (Carvajal syndrome) showed no keratoderma; it was suggested that, in this case, either DSP binding to IF is reduced but not lost or that loss of desmosomes-IF binding via DSP could be compensated for by other desmosomal proteins.

It is possible that absence of skin defects in heterozygous carriers of DSP missense mutation S299R can be explained by considering that this mutation does not affect DSP-IF binding, which, on the contrary, is targeted by other mutations producing a keratoderma phenotype.

In heterozygotes for the S299R mutation, the majority of desmosomal cadherin-JUP complexes would be defective because of the dimeric nature of DSP functional molecules. This would explain the dominant pattern of inheritance of the disease caused by such mutation.

Recessive arrhythmogenic right ventricular dysplasia

In this syndrome, beside cardiac alteration skin and hair alterations are present. Affected subjects present a severe form of the disease and the clinical heterogeneity that is typical of ARVD type 8 is not present. The disease is due to a recessive mutation in DSP gene. The mutation described in this syndrome consists in a substitution of the glycine in position 2375 to a positively charge arginine (G2375R). It is quite likely that this mutation alters the B segment and disrupts the DSP-IF interaction.

Mutations in desmosomal proteins causing a syndrome with cardiac, hair, and skin abnormalities have been described. Naxos disease is an autosomal recessive condition where the affected gene is JUP. Both DSP and JUP are important components of desmosomes. Desmosomes are symmetrical disc-shape intracellular junctions found primarily in epithelial tissue. They mediate adhesion between cells and link the IFs of neighboring cells, thus establishing an integrated framework across the entire tissue.

Defects in DSP, and autoantibodies to DSP, have been described in various skin disorders, particularly palmoplantar keratodermas, skin blistering diseases such as autoimmune pemphigous and other pemphigous-related disorders. Desmosomal involvement was described in infectious skin diseases as in bolus impetigo and in staphylococcal scalded-skin syndrome.

Naxos disease

Naxos disease is an atypical ARVD form in two aspects: the pattern of inheritance is autosomal recessive rather than dominant, and, in addition to cardiac manifestations of ARVC/D, patients exhibit diffuse non-epidermolytic palmoplantar keratoderma and woolly hair. Deletion of two base pairs (2157 and 2158) in the gene encoding JUP on chromosome 17q21 produces a frameshift, which alters five amino acids and then prematurely terminates translation.

This mutation is thought to disrupt a PKC phosphorylation site which is involved in JUP binding and in clustering of desmosomal cadherin-JUP complexes. Altered integrity at cardiac myocyte cell-cell junctions may promote myocyte degeneration and death, with the repair process consisting of replacement of myocardium by adipose and fibrous tissue.

In addition, JUP has been shown to play a direct role in regulating apoptotic cell death. The incidence of the disease is high in a relatively small region. Many families with this syndrome have been identified in Naxos and in other Cyclads islands. It is quite likely that the inhabitant isolation had a role in the spreading of the disease, also considering the recessive inheritance. On the contrary, the incidence of ARVC/D type 8 form is unknown at the moment, also due to the fact that this form does not differ clinically from the other forms of the disease. Thus it is not possible to pre-select patients due to clinical data in ARVC/D8, whereas in Naxos syndrome and in ARVD type 25 the presence respectively of palmoplantar keratosis and effort-induced arrhythmias allow a pre-selection of subjects.

Carvajal syndrome

This syndrome, described from Norgett in 2000, is characterized by a dilated cardiomyopathy associated with skin and hair disorders. The clinical manifestations are similar to the recessive form of ARVD, thus it cannot be excluded that these are similar diseases due to different mutations of DSP. In addition also this disease is recessive.

In conclusion these four types of diseases are a clear evidence that a similar cause can provoke myocyte necrosis. The involvement of two desmosomal proteins (DSP and JUP) in different ARVD/C clinical phenotypes suggests that some ARVD/C might result from defects in intercellular connections. According to present knowledge, mechanical forces applied to adherens junctions activate stretch-sensitive calcium-permeable channels via cadherins' mechanical intracellular signaling.

Moreover, stretching of cardiomyocytes is known to modulate the elementary calcium release process from ryanodine receptor release channels. Therefore, a genetically impaired response to mechanical stress might adversely affect intracellular calcium concentration and the excitation-contraction coupling. In addition, it might induce apoptosis and cellular necrosis, which, in turn, would promote fibrosis and adipose substitution, as in several muscular dystrophies. The almost selective affection of the right ventricle might be in relation to its extensibility, in comparison with that of left ventricular free wall. It is interesting to notice that mutations in cardiac ryanodine receptor cause dominant ARVC/D type 2, thus supporting the hypothesis of a key pathogenic role played by altered intracellular calcium concentration in these diseases.

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Does implantable cardioverter-defibrillator therapy modify the natural history of arrhythmogenic right ventricular cardiomyopathy?

Domenico Corrado, Loira Leoni, Gianfranco Buja*, Gaetano Thiene*, on behalf of the Investigators of the Defibrillator in Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia in North Italy (DARVIN) Study (see Appendix)

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Introduction

The natural history of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is strongly related to ventricular electrical instability which can precipitate sudden arrhythmic death mostly in adolescents and young adults[1-4]. Heart failure is rare and occurs later during the disease course as a result of progression of the right ventricular disease and left ventricular involvement[4]. ARVC/D has become an emerging indication for defibrillator to prevent sudden arrhythmic death in the setting of cardiomyopathies[5]. Although there is definitive clinical evidence that the defibrillator is the most effective therapy for both primary and secondary prevention of sudden death in patients with coronary artery disease[6-8], there are very few published data on efficacy and safety of such a therapy in patients with ARVC/D, mostly because of the relatively low prevalence of the disease in the general population and the relatively low event rate[9-11]. Current indications for defibrillator implantation in patients with ARVC/D are empiric and based widely on the experience gained by different centers using analogies with other conditions requiring antiarrhythmic therapy[12]. Since identification of clinical findings that predict clinical outcome has been elusive there is a growing tendency to implant defibrillators indiscriminately once the disease has been diagnosed regardless of risk stratification[12].

Further, major concerns have been raised on the risk of perforation due to the lead implantation into a thin right ventricular free wall as well as on the difficulty to maintain adequate sensing and pacing thresholds during the follow-up due to the progressive loss of the right ventricular myocardium[10,12].

In this chapter we review the available studies addressing the efficacy and safety of implantable cardioverter-defibrillator (ICD) therapy in patients with ARVC/D, with particular reference to the DARVIN study[13] which is the first to address the clinical impact of ICD therapy in changing the natural history of ARVC/D in a relatively large patient population treated for both secondary and primary prevention of sudden death.

Previous studies

Breithardt et al.[9] in 1994 reported 18 patients with ARVC/D who received an ICD because of drug refractory ventricular tachycardia (VT) or ventricular fibrillation (VF) or previous cardiac arrest without reproducible induction of VT or VF. Only the initial patient received an epicardial lead system, whereas in the subsequent 17 patients a transvenous approach was used. Among these patients, 12 received a transvenous subcutaneous system and the remaining 5 received a purely transvenous lead system. Thirteen of the devices implanted had antitachycardia pacing capabilities. Although there were no serious perioperative complications, a major problem was the placement of the transvenous lead, which required testing of two or more positions (range 2 to 9; median 4) in 10 of 17 patients (59%) to achieve satisfactory sensing and pacing results. During a follow-up of 17 ± 11 months, 9 of the 18 patients (50%) experienced a total of 130 episodes of appropriate ICD therapies that ranged from 1 to 40 episodes per patient (median 11 episodes). Because of the high rate of the tachycardia or the inability of the device to perform antitachycardia pacing, 59 of these 130 episodes (45%) were terminated by shock therapy, whereas the remaining 71 episodes (55%) were effectively terminated by antitachycardia pacing.

Link et al.[10] reported on 12 patients with ARVC/D who were treated with ICD. The mean age was 31 ± 9 years (range 15-48 years). Patients presented with presyncope (n = 5), syncope (n = 4), or cardiac arrest (n = 3). During programmed electrical stimulation 9 patients had sustained VT, while 3 patients had no inducible arrhythmia. Transvenous leads were placed in 9 patients. In these patients pacing thresholds were significantly higher, R-wave amplitudes were significantly lower, and defibrillation thresholds were not significantly different than in a cohort of patients without ARVC/D. There were no acute or chronic complications of right ventricular lead placement. Follow-up averaged 22 ± 13 months (range 1-45 months). There was one sudden death at 1 month of follow-up. Of the 12 patients, 8 have had appropriate therapy delivered by the ICD. Six patients received sotalol to reduce the frequency of ICD discharges.

Tavernier et al.[11] described 9 consecutive patients (8 male and 1 female, mean age 36 ± 18 years) with ARVC/D presenting with VT and hemodynamic collapse (n = 6) or VF (n = 3), treated with an ICD. After a mean follow-up of 32 ± 24 months, all patients were alive. Six patients received a median of 19 (range 2-306) appropriate ICD interventions for events detected in the VT window; 4 received a median of 2 (range 1-19) appropriate ICD interventions for events detected in the VF window. Inappropriate interventions were seen for sinus tachycardia (18 episodes in 3 patients), atrial fibrillation (3 episodes in 1 patient), and for non-sustained polymorphic VT (1 episode in 1 patient).

The DARVIN Study

The DARVIN Study is an observational, multicenter study aimed to determine the efficacy and safety of ICD therapy, exclusively based on stored electrograms by the device, in a large patient population with ARVC/D at high risk for sudden death[13]. The study population consisted of 132 patients (93 males, 39 females, mean age 40 ± 15 years) who were recruited at 22 institutions in North Italy and at one in the United States (see Appendix). In 95 patients (78%), indications for ICD implant were a history of either cardiac arrest or sustained ventricular tachycardia (secondary prevention group); the other 37 (22%) had one or more risk factors for sudden death in the absence of spontaneous ventricular tachyarrhythmias (primary prevention group). During a mean follow-up of 39 ± 25 months, there were 3 deaths: one sudden, one due to infective endocarditis, and one to congestive heart failure. Sixty-four patients (48%) had at least one appropriate ICD intervention, 21 (16%) had inappropriate interventions, and 19 (14%) had ICD-related complications. Fifty-three of the 64 patients (83%) were receiving antiarrhythmic drugs at the time of the first appropriate discharges: 28 received sotalol, 13 beta-blockers, 11 amiodarone (alone in 5 and in association with beta-blockers in 6), and one flecainide. Analysis of the stored electrograms showed that 32 patients (24%) experienced VF or flutter which in all likelihood would have been fatal in the absence of the device. The VF/flutter-free survival rate was 72% at 36 months compared with the actual patient survival of 98% ($p < 0.001$). The incidence of VF /flutter was similar in both primary and secondary prevention groups (7.0 vs 7.4% per year). Patients implanted because of hemodynamically stable VT had a significantly lower incidence of VF/flutter (log rank = 0.017). History of cardiac arrest or hemodynamically unstable VT, young age, and left ventricular involvement were independent predictors of VF/flutter.

Therefore, the major findings of the DARVIN Study were that during a mean 3.3 year follow-up, approximately 50% of the 132 patients had at least one appropriate defibrillator intervention, despite antiarrhythmic therapy. Further, 24% of the total patient population experienced one or more episodes of VF/flutter, documented by stored intracardiac ECG data, that in all likelihood would have been fatal in the absence of the device therapy. Analysis of risk factors showed that a younger age, a history of cardiac arrest or hemodynamically unstable VT, and left ventricular involvement were independent clinical variables associated with the occurrence of such life-threatening arrhythmias. On the contrary, therapy with defibrillator did not improve survival in the subgroup of patients presenting with hemodynamically stable monomorphic VT.

The high incidence of defibrillator interventions in the DARVIN Study is in agreement with data from the small series of patients with ARVC/D previously report-

ed by Breithardt et al.[9] (9 of 18 patients, 50%), Link et al.[10] (8 of 12 patients, 67%), and Tavernier et al.[11] (7 of 9 patients, 78%). Precise data on the efficacy of ICD in comparison with antiarrhythmic therapy cannot be derived from this non-randomized study. However, the majority of appropriate interventions and 53% of shocks on VF/flutter occurred despite concomitant antiarrhythmic therapy with beta-blockers and/or class III antiarrhythmic drugs. This finding highlights that the protection provided by the defibrillator against sudden death is considerably superior.

The analysis of the incidence of defibrillator interventions that were triggered by VF/flutter suggests a significant improvement in survival thorough the follow-up, with an actual patient survival rate of 96% compared with a 72% VF/flutter-free survival rate at 36 months ($p < 0.001$).

In the DARVIN Study patients who received prophylactic defibrillator for primary prevention (i.e. patients with one or more risk factors but without spontaneous sustained ventricular tachyarrhythmias) had a similar incidence of appropriate interventions triggered by VF/flutter as did patients with a history of aborted sudden death or sustained VT (7.0 vs 7.4% per year, respectively). Although any definitive recommendation on defibrillator implantation cannot be made with regard to primary prevention of sudden death, the finding that appropriate defibrillator therapy distinctively occurred in patients who were implanted because of two or more risk factors is relevant for risk stratification.

It is noteworthy that the DARVIN patient population is a high-risk subgroup of ARVC/D patients that are not comparable with most patients with the disease who can be either no treated or treated effectively with antiarrhythmic drugs due to the low arrhythmic risk[14,15].

In the DARVIN Study there was a lower rate of both inappropriate defibrillator interventions and complications than previously reported. Inappropriate therapy occurred in 16% of patients in the present study, compared with 33% of those reported by Link et al.[10], and 44% of patients in the study of Tavernier et al.[11]. This discrepancy may be explained by the larger use of beta-blockers and sotalol, which reduced the number of inappropriate interventions on both sinus tachycardia and supraventricular tachyarrhythmias. Moreover, nearly one fourth of DARVIN patients had dual-chamber detection algorithms that improved discrimination of ventricular from supraventricular arrhythmias. With regard to complications, it is interesting to note that during the follow-up 5 patients required an additional septal lead because of loss of ventricular sensing/pacing functions, most likely because of progressive replacement of the right ventricular myocardium by fibrofatty tissue.

The DARVIN Study design was that of a retrospective survey of 22 collaborative medical centers with possible limitations in patient selection. This suggests the need for a prospective controlled study with total mortality as primary endpoint in order to conclusively define the survival benefit of defibrillator implantation in patients with ARVC/D and its superiority over other therapeutic modalities. However, for any inheritable cardiac diseases such as hypertrophic cardiomyopathy[16], cardiac ion channel diseases[17,18], and ARVC/D, a prospective-randomized study design is difficult to perform due to ethical reasons and practical limitations predominantly linked to relatively low disease prevalence and low event rate. To this regard a 10-year interval was required to generate the data on 132 patients. Since many years will be required to complete a prospective evaluation in the use of defibrillators in ARVC/D patients, the DARVIN data will be the best available for some time regarding the efficacy/safety of ICD in this disease.

Conclusions

The recent DARVIN Study demonstrated that ICD therapy has a significant impact on the natural history of ARVC/D and provides life-saving protection by effectively terminating VT or VF in affected patients. The available data support the prophylactic use of ICD in ARVC/D patients for both primary and secondary prevention of sudden death.

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Appendix

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NON-CONTACT MAPPING LOOKS INTO THE DIFFERENT MECHANISM OF RIGHT VENTRICULAR ARRHYTHMIA

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Introduction

In patients with ventricular tachycardia (VT) originating from the right ventricle, the understanding of the arrhythmia mechanism is critical to define the therapeutic approach: while idiopathic arrhythmia related to enhanced automatism in the right ventricular outflow tract is characterized by a benign long-term prognosis, patients with VT due to a reentry mechanism in the setting of arrhythmogenic right ventricular dysplasia (ARVD) suffer from a high rate of long-term VT recurrences and implantation of a cardioverter-defibrillator is often required to prevent sudden death[1].

While current imaging techniques (echocardiography, magnetic resonance imaging, right ventricular angiography) can detect structural abnormalities in the right ventricular wall in patients with an overt form of ARVD, minor subtle alterations may be found in patients with the so-called "idiopathic" arrhythmia. The evaluation of the arrhythmogenic substrate in patients belonging to this "gray zone" is particularly relevant as no long-term follow-up data are available to guide a proper treatment strategy.

Some recently published data[2,3] suggest that several clinical and electrophysiological features are helpful in discriminating patients with benign idiopathic arrhythmias from those with reentry related VTs, including familiar history, symptoms, sinus rhythm 12-lead ECG, spontaneous arrhythmia morphology, inducibility by programmed electrical stimulation and number of induced VTs (Table I).

Recent data suggest that activation mapping or electroanatomical mapping can show the presence of scarred or abnormal myocardium in patients with VT in the setting of ARVD[4], and that the lack of abnormalities at

Table I. Differences between arrhythmogenic right ventricular dysplasia (ARVD) and idiopathic ventricular tachycardia (VT) patients.

	Idiopathic right ventricular VT	ARVD VT
Malignant arrhythmia familiar history	No	May be present
Symptoms	Palpitations	Palpitations, dizziness, syncope, cardiac arrest
Sinus rhythm 12-lead ECG	Normal	RBBB complete or incomplete, epsilon wave, negative T wave V_1-V_4
Spontaneous ectopy	Monomorphic, LBBB-inferior axis	Monomorphic, LBBB. Inferior, intermediate or superior left axis. Polymorphic
Spontaneous arrhythmia pattern	Ectopies, non-sustained VTs	One or more different sustained monomorphic VT
Sinus rhythm mapping	Normal amplitude and duration electrograms in the right ventricle. Discrete late spikes in RVOT without fragmentation	Low-amplitude, fragmented and late electrograms in one ore more areas in the right ventricle
Behavior of induction	Never inducible by PES. Spontaneous arrhythmia sometimes after fast overdrive pacing from the right ventricle. Catecholamines often required	Inducible by PES
No. induced morphologies	None or clinical arrhythmia	Non-clinical morphologies frequently induced
Activation mapping during VT	Discrete presystolic spike at about -20 ms before the earliest QRS onset	Diastolic fragmented electrograms or diastolic potentials

LBBB = left bundle branch block; PES = programmed electrical stimulation; RBBB = right bundle branch block; RVOT = right ventricular outflow tract. From Niroomand et al.[3], modified.

right ventricular mapping and VT inducibility are predictive of a long-term benign course[3].

Whether sinus rhythm mapping of the right ventricle may enhance the predictive value of imaging techniques in the assessment of patients with right VT is currently unclear.

Ablation of ventricular tachycardia

Conventional activation mapping may guide catheter ablation of idiopathic or ARVD VTs.

As previously described, in idiopathic VT, a distinct left bundle branch block-inferior axis pattern is present and the arrhythmia is almost always not inducible by programmed stimulation or inducible only by rapid ventricular pacing. Isoproterenol infusion is often useful to enhance inducibility; most frequently the arrhythmia occurs as non-sustained repetitive runs rather than sustained VT episodes.

Discrete presystolic sharp spikes preceding by about 20 ms the earliest QRS onset can be found by conventional activation mapping of the outflow tract; isolated diastolic potential or clear diastolic activity are invariably absent.

Pacemapping is useful to assess the correct location of the focus by comparing the surface QRS morphology of spontaneous arrhythmia to that of the paced beats from different sites of the right ventricular outflow tract.

A discrete, high voltage electrogram with a late sharp spike but without any fragmentation can be found during sinus rhythm at the ablation site.

During radiofrequency delivery on the ablation site, the occurrence of fast VT burst proves that radiofrequency is applied on sites where firing activity is present. Sudden spontaneous arrhythmia cessation occurs after successful abolition of the ectopic focus. About 90% of these patients are free from arrhythmia recurrences after successful catheter ablation.

The variable occurrence of spontaneous ectopy at the time of mapping can be a cause of ablation failure when conventional techniques are used. In this setting, the use of non-contact mapping, allowing detection of the site of origin of a single ectopic beat, increases the accuracy of mapping and the long-term success rate. In our experience, favorable long-term prognosis was achieved in 32/41 patients (78%) treated by conventional mapping[3]; on the other hand, 36/40 patients after non-contact mapping procedure were found on a stable sinus rhythm at follow-up. In patients with ARVD multiple VT morphologies are often induced by programmed stimulation. The QRS morphology is characterized by different patterns of deviation in the limb leads (that is, left bundle branch block-inferior axis is not specific for idiopathic VT) reflecting the location of the reentry circuit that may involve the right ventricular outflow tract, apical free wall, septal and basal peritricuspidal free wall.

Activation mapping can demonstrate isolated diastolic potentials or fragmented electrogram with early diastolic activation preceding QRS onset. Entrainment techniques are useful to assess the functional role of each mapped area in the reentry circuit. In epicardial or deep septal VT endocardial early activity is absent or late.

As non-tolerated VTs are frequently induced, the acute success rate of catheter ablation is lower (about

70% of induced VT) and the recurrence rate is high as only 20 to 40% of patients remain free from VT recurrence over the long term.

Non-contact mapping allows mapping of non-sustained or non-tolerated arrhythmia by reconstructing on a virtual geometry the activation sequence of a single beat. Inconsistent idiopathic arrhythmias and non-tolerated VTs may be mapped and ablated using non-contact mapping. The arrhythmia mechanism (focal or reentry) can also be clearly assessed by non-contact mapping, as focal mechanism is characterized by the absence of detectable diastolic activity (or just slight presystolic activity) before the exit, while in reentry arrhythmias a clear diastolic low-voltage activation may often be recognized (Figs. 1 and 2).

Electroanatomical mapping requires at the moment long-lasting stable arrhythmias and is not useful to map fast or non-sustained VTs. It may also identify areas of abnormal propagation in sinus rhythm and define activation pattern during stable VT.

Non-contact mapping and electroanatomical mapping may be used to define an ablation line crossing the VT diastolic pathway or to encircle the exit point. Also linear lesions aimed to disconnect scarred myocardium to the surrounding normal areas may be performed. Further studies are evaluating whether these newer approaches will improve the long-term outcome especially in the setting of ARVD VTs.

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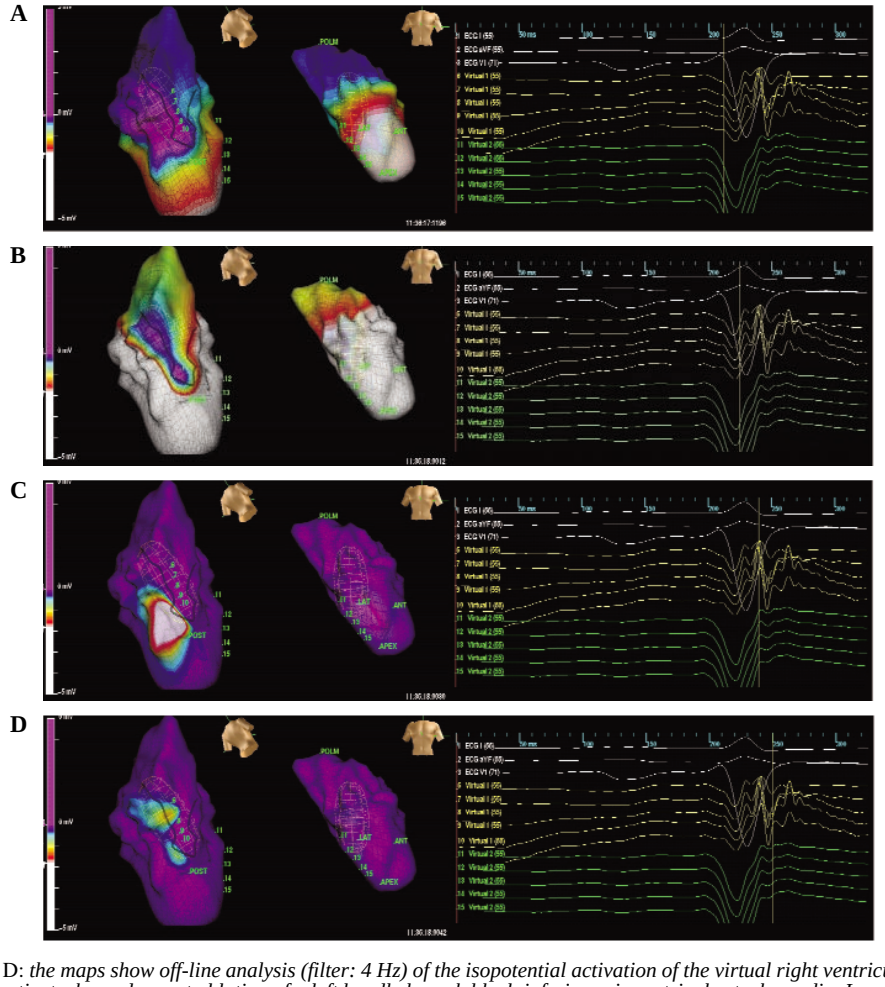

Figure 1. Panels A *to* D: *the maps show off-line analysis (filter: 4 Hz) of the isopotential activation of the virtual right ventricular chamber during a sinus rhythm beat of a patient who underwent ablation of a left bundle branch block-inferior axis ventricular tachycardia. Imaging failed to demonstrate structural abnormalities diagnostic of arrhythmogenic right ventricular dysplasia. Differences in local virtual electrogram amplitude are shown by color codes on the left side of each map. Right ventricular activation wave originates from the right ventricular apex and spreads through the right ventricular free wall; conduction block occurs at basal posterolateral free wall. Delayed activation of this area is shown in* panels C *and* D. *The pattern of local abnormal activation is demonstrated by fragmented and low-amplitude electrograms (virtual 6 to 10) within this area.*

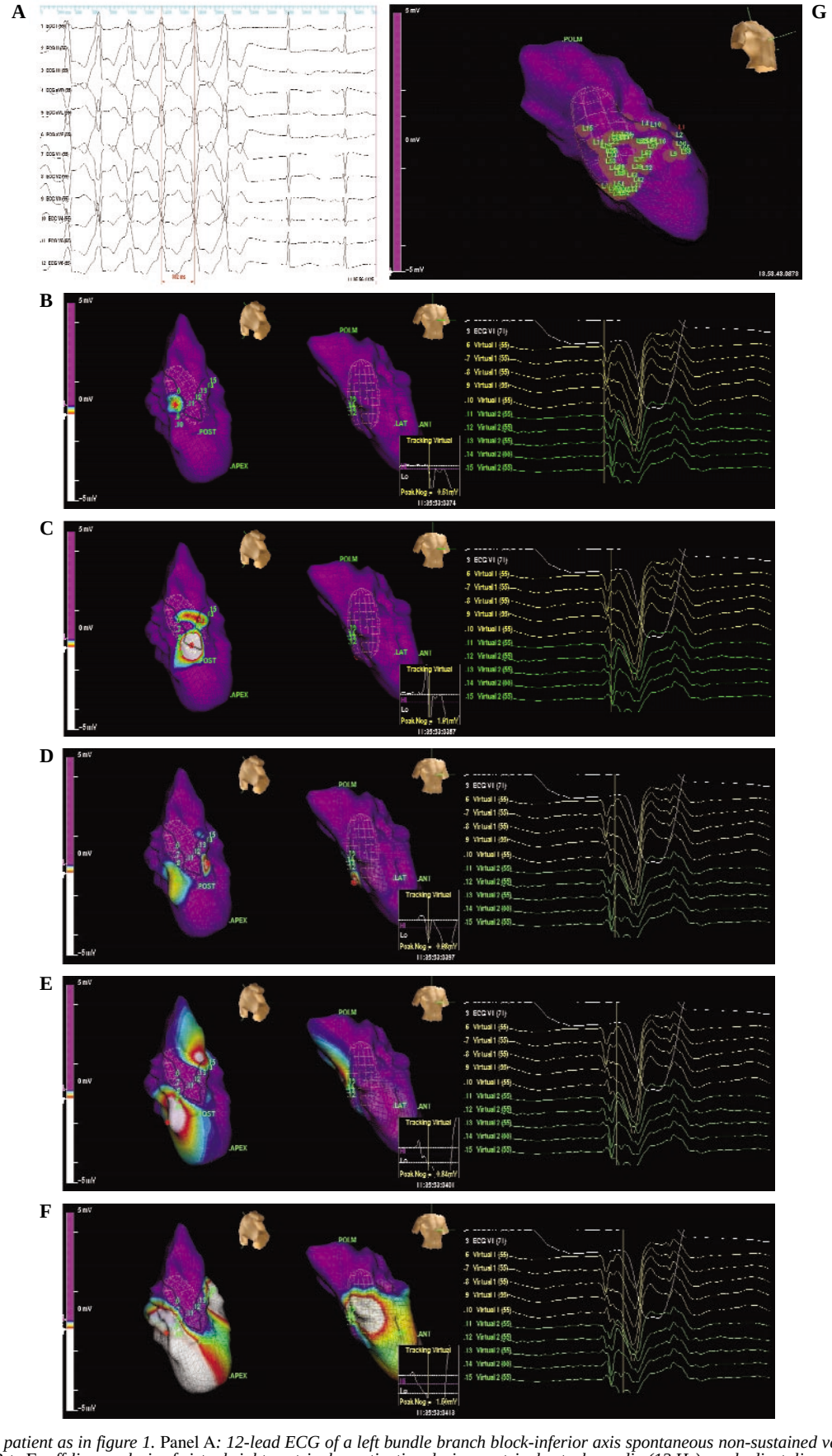

Figure 2. *Same patient as in figure 1.* Panel A*: 12-lead ECG of a left bundle branch block-inferior axis spontaneous non-sustained ventricular tachycardia.* Panels B *to* F*: off-line analysis of virtual right ventricular activation during ventricular tachycardia (12 Hz); early diastolic activity, characterized by fragmented virtual electrogram preceding QRS onset, is present on scar border zone and within the scar. Diastolic activity simultaneously spreads anteriorly and laterally in the scar (*panels B-D*). Two different exit points (anterior and lateral) are demonstrable (*panels E *and* F*).* Panel G*: multiple radiofrequency lesions are placed within the scar to interrupt impulse propagation over the diastolic pathway. The procedure resulted in the prevention of induction of any further ventricular tachycardia.*