Implantable Cardioverter Defibrillator in Arrhythmogenic Right Ventricular Cardiomyopathies

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In the present issue of *Circulation*, Wichter et al report the largest single-center experience demonstrating the benefit of implantable cardiac defibrillators (ICDs) in the treatment of patients with arrhythmic right ventricular cardiomyopathy (ARVC). The patients seem well defined, and they meet the task force criteria. In addition, 50 of 60 patients have had the diagnosis confirmed by endocardial biopsy. Advances in molecular biology and genetics, however, suggest that the term ARVC encompasses a large spectrum of diseases with similar clinical presentations and histological features. This was discussed in part in a previous editorial in *Circulation*. Recent information suggests that there is an overlap in the different forms of diseases included under the general term ARVC.

**Terminology**

The term *right ventricular cardiomyopathy*, which was introduced by the World Heart Federation and World Health Organization in 1996 in the new classification of cardiomyopathies, was selected to encompass arrhythmogenic right ventricular dysplasia (ARVD) and several other clinical entities, some of them known by a different name. In the classical article by Marcus et al, the term *right ventricular dysplasia* was taken from a book chapter on reentrant arrhythmias published in 1977. This work reported the results of antiarrhythmic surgery in young male patients with good left ventricular function who had ventricular tachycardia (VT) originating in the right ventricle. The term *dysplasia* was chosen because the right ventricle of 3 operated patients was covered by fat. The remaining myocardium was present only in the subendocardium. This striking feature, which suggested the replacement of myocardium by fat, was strengthened by microscopic examination that showed strands of cardiomyocytes bordered by or sometimes embedded in fibrosis or adipose tissue. It was suspected that myocardial replacement by fat and fibrous tissue started early in life, possibly in the embryo. This concept was reinforced by a report of the heart of a 24-week-old fetus with arrhythmias in utero. The role of apoptosis was also demonstrated as one of the factors contributing to myocardial remodeling in ARVD.

**Molecular Biology**

In recent years, an extended classification of subgroups of these right ventricular cardiomyopathies has been proposed on the basis of genetic studies. This information may impact the selection of patients for ICD therapy on the basis of genotype-phenotype relationship. Among them, Naxos disease was particularly informative because this inherited condition with a recessive form of transmission is associated with clinically obvious ectodermal dysplasia (keratoderma, woolly hair) and has the typical histological pattern of ARVD. This association prompted the identification of a nonsense mutation of a gene coding for a protein (plakoglobin) that could explain both ectodermal manifestations and cardiac dysplasia. In another form of the disease identified in Ecuador, presenting clinically as idiopathic dilated cardiomyopathy without fatty infiltration, a mutation of a gene coding for a protein in the same category of cell–cell adhesion (desmoplakin) was discovered, and a mutation on the gene encoding for desmoplakin was identified in the Veneto region of Italy in a familial dominant form of ARVD. A third genetic abnormality was identified in Italy in patients with a familial dominant form of exercise-induced ventricular arrhythmia. In these patients, however, the mutation involved the sarcoplasmic reticulum calcium release channel (ryanodine receptor).

The right ventricular ST-segment elevation (Brugada syndrome) frequently associated with signs of delayed conduction in the right bundle branch is due to a cardiomyopathy in some cases. This syndrome carries the risk of nocturnal sudden death, particularly in young adults. Arrhythmic death is not prevented by antiarrhythmic drugs, with the possible exception of quinidine. The sodium channel (SCN5A) was originally involved in 50% of the patients studied. However, the relation between the Brugada syndrome and ARVD is not always clear. Examination of the pathological material in patients with the Brugada syndrome who died suddenly showed that one third had structural heart disease, consisting of fat and fibrosis strongly suggestive of ARVD and/or signs of inflammation. A systematic study of a group of 60 ARVD patients in our center showed that 26% had ST-segment elevation ≥1 mm in leads V1 through V3. Therefore, there is a significant overlap between ARVD and Brugada syndrome that needs further investigation.

Another form of ventricular arrhythmia frequently observed in the young is right ventricular outflow tract (RVOT)
VT. A few patients who have benign ventricular extrasystoles arising from the RVOT may develop rapid VT degenerating into ventricular fibrillation. These patients are candidates for the implantable defibrillator. However, ablation of the arrhythmic focus involving the Purkinje system was able to prevent recurrence of life-threatening arrhythmias. In addition, the autopsy material in one case of RVOT demonstrated the presence of fat and fibrosis in surviving fibers, plus signs of inflammation in the infundibular area, which suggested a localized form of ARVD.

**Antiarhythmic Drugs**

In the article by Wichter et al,1 antiarrhythmic drugs were used in 32% after ICD implantation and in 48% at the end of the study. However, only 2 patients were given a drug combination. One could speculate that the rate of appropriate ICD discharges, including those for antitachycardia therapy, might be lower than reported in this series if a combination of antiarrhythmic drugs were used. In our experience, the most effective combination is the combination of amiodarone plus β-blocking drugs, as used in the Canadian Amiodarone MI Arrhythmia Trial (CAMIAT) and European Myocardial Infarct Amiodarone Trial (EMIAT). In patients with good left ventricular function, the combination of flecainide with sotalol may be used. One could speculate whether the number of appropriate ICD discharges would have been substantially reduced in a cohort of patients treated with these drug combinations. The answer to this question will require a prospective standardized trial of antiarrhythmic drug combination in patients with ARVD implanted with ICDs.

**Equipment Effectiveness**

The study demonstrates that the ICD therapy is an effective treatment even though it was not a study randomizing patients to ICD treatment or antiarrhythmic drug treatment. Only 2 patients died of an arrhythmia over 80 months. The study also illustrates that ICD therapy is not without its complications in the treatment of the disease. A relatively high incidence of complications would be expected during long-term follow-up of relatively young patients. In addition, a complication that was rather common and almost unique to the treatment of this disease by ICD is the higher pacing thresholds and lower amplitude of endocardial potentials because of diffuse involvement by fat and fibrosis of the right ventricle at the site of ICD lead placement. The implanter needs to be aware of this problem and prepared to use alternative sites, including active fixation of the electrode in the septum, which is generally not involved in this disease process. In addition, this situation may worsen with time because of disease progression and dilatation of the right ventricle. Because these patients are in the younger age group, it is anticipated that they will need several generator replacements and are likely to have one or more lead changes, as well as lead fracture and premature battery exhaustion. The use of modern leads with the same diameter (isodiametric lead) will greatly facilitate lead withdrawal.

In the report by Wichter et al,1 there is no mention of high defibrillation thresholds. However, we are aware of high defibrillation thresholds in patients with ARVD as well as in the Brugada syndrome. The reason for this situation is unknown. Of note, there is very little right ventricular free wall perforation reported in ARVD. This potential complication would have been expected because of the thinness of right ventricular free wall in ARVD.

**Indications for ICD in ARVD**

A major clinical question that was not completely addressed in this study was whether it would be possible to identify with a high degree of certainty those patients with ARVD who would benefit from ICD implantation on the basis of anticipated knowledge of those who would have an arrhythmic cardiac death. With good left ventricular function, many patients with ARVD can tolerate a rapid ventricular rate, even exceeding 240 bpm, without syncope or near syncope. An alternative analytic approach would be to restrict the high-risk group to those individuals who have VT and who have had syncope or near syncope.

The most frequent and difficult problem in deciding who requires an ICD relates to family members. Wichter et al found that electrophysiological study positive for the induction of fast unstable VT/ventricular fibrillation is an independent predictor of life-threatening events during follow-up. Therefore, it is tempting to deduce that VT induction in a family member can be valuable for identifying individuals at risk.

It is hoped that it will be possible to identify patients with ARVD at risk of sudden cardiac death by noninvasive techniques, such as advanced methods of electrocardiography and echocardiography, and invasive approaches, such as electrophysiological study and contrast angiography.

It is also hoped that these questions about risk stratification and indication for ICD therapy in high-risk subgroups of right ventricular cardiomyopathies will be answered with the help of registries. More data prospectively collected from many centers are needed to answer the important questions, on the basis of clinical presentation, genetics, and baseline characteristics, as to who would require ICD therapy. It is hoped that this information will be forthcoming from the two major ARVD registries, the European and the North American Registries. Physicians are encouraged to enter their patients suspected of ARVD into these registries so that we will be able to make a judgment of who requires ICD therapy on the basis of prospectively collected data from a large number of patients.

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**References**


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