The Therapeutic Role of the Implantable Cardioverter Defibrillator in Arrhythmogenic Right Ventricular Dysplasia

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Arrhythmogenic right ventricular dypslasia (ARVD) is a cardiomyopathy characterized by right ventricular (RV) cardiac myocyte atrophy with subsequent fibrofatty infiltration and replacement. This pathophysiological process provides a healthy substrate for the development of electrical instability, eventually resulting in the development of ventricular tachycardia (VT) and/or ventricular fibrillation (VF), and thus sudden cardiac death (SCD), all too often in younger patients or competitive athletes. Many patients first come to medical attention due to malignant ventricular arrhythmias.

Long-term studies evaluating the efficacy of pharmacological therapy have not been promising. This may in part be due to the fact that drug therapy has been implemented more for alleviating various symptoms such as palpitations. Moreover, pharmacological therapy is also often empirical. Invasive catheter-based therapy has been utilized with some degree of success, however has not been shown to provide protection against SCD.

The implantable cardiac defibrillator (ICD) has emerged as a reliable ally in the primary prevention of SCD in the setting of ischemic cardiomyopathy and heart failure and for secondary prevention of SCD as well, however published data on the safety and efficacy of this therapy in ARVD has been sparse. We sought to review the recent published data on the role of the ICD among patients with ARVD.

Short Term Results of ICD Therapy

A handful of studies evaluating the short-term use and efficacy of the ICD in ARVD patients have been promising. Tavernier et al studied the outcome of 9 ARVD patients treated with a single chamber ICD for ventricular tachyarrhythmias presenting following VT with hemodynamic failure (6) and VF (3) over 32 months. All patients had previously failed pharmacologic therapy and/or catheter ablation therapy for VT. Eight patients received antiarrhythmic therapy immediately following ICD implantation.

At the conclusion of follow-up, all patients were alive. One patient experienced repeated episodes of VT with worsening HF and eventually underwent cardiac transplantation. Seven patients received at least one appropriate ICD intervention but 4 patients received at least one inappropriate ICD intervention. A cumulative 442 appropriate ICD interventions (antitachycardia pacing [ATP] and/or cardoversions) occurred among 7 patients (78%). The results demonstrated a high arrhythmia recurrence rate but a good overall prognosis despite frequent inappropriate interventions.

Similarly, Link et al examined 12 ARVD patients treated with ICDs. Patients presented with cardiac arrest, syncope and presyncope. VT was the presenting arrhythmia in 7 of 12 patients and most (75%) patients failed antiarrhythmic therapy. After a mean follow up period of 22 $\pm$ 13 months, there was one SCD. Eight (66%) patients had appropriate therapy, similar to previous series, delivered by the ICD in the form of CV (46) and ATP (105). Due to frequent ICD therapy, sotalol was added to six patients and less arrhythmic activity was noted. 4 (33%) patients experienced inappropriate discharges from sinus or supraventricular tachycardia and lead fractures. It was concluded that ICD therapy in this patient population was feasible and safe.

Long Term Results of ICD Therapy

More recently, larger multicenter trials have examined the role of the ICD in ARVD patients over extended periods of time.

Corrado et al examined the efficacy of the ICD among 132 ARVD patients over a period of 3.3 years. The clinical indications for ICD implantation were cardiac arrest, sustained VT with hemodynamic compromise, unexplained syncope and a family history of SCD. During follow up, there were 4 deaths (3%) from recurrent ventricular arrhythmia, complications from ICD implantation, and worsening HF. 64 (48%) patients had appropriate ICD interventions for episodes of ventricular tachyarrhythmias, including

29 (45%) patients who experienced more than 5 interventions or VT storm. Most (83%) of the patients with appropriate interventions were receiving concomitant antiarrhythmic drug therapy at the time of ICD intervention. The incidence of ICD discharges did not differ between patients who did and did not receive antiarrhythmic drug therapy irrespective of clinical presentation. The rate of appropriate ICD discharge was found to be 15% per year. Inappropriate ICD events occurred in 21 (16%) patients and 19 (14%) patients had nonfatal ICD device or lead complications. Analysis of stored electrocardiograms showed that 32 patients (24%) experienced VF/V-flutter that was successfully recognized and terminated by the device. Survival rates were 99% at 12 months, 98% at 24 months, and 96% at 36 months follow-up and freedom from VF/V-flutter were 88%, 79% and 72% at similar time points. At the 36-month mark the estimated overall survival of the general population matched for age, gender and race was 99.5%. A prior history of cardiac arrest, VT with hemodynamic compromise, decreasing age and decreasing LV ejection fraction were defined as statistically significant predictors for ventricular arrhythmia. The major finding of this study was that nearly half of the patients had at least one episode of ventricular tachyarrhythmias that necessitated ICD intervention despite the use of antiarrhythmic drug therapy. Another important finding was that most ARVD patients treated with ICDs were younger (mean age 40 $\pm$ 15 years), therefore the long term survival benefits conferred by the ICD are likely to be greater in ARVD patients as opposed to those with a history of coronary disease with poor LV dysfunction.

Wichter et al examined ICD-based therapy in 60 ARVD patients over 80 $\pm$ 43 months. Slightly more than half of the patients were on antiarrhythmic drug therapy at the time of ICD implant. During the follow up period of up to 12 years, 8/60 (13%) patients died from SCD or heart failure. Survival rates at 5 and 10 years were 94% and 76%, respectively. Appropriate ICD therapy was observed in 39/56 (70%) patients in the form of cardioversion and/or ATP. Actual appropriate ICD therapy was 26% at 5 years follow-up. Similar to other studies, Multivariate Cox regression analysis identified extensive RV

dysfunction (odds ratio, 2.09; 95% CI, 1.03 to 4.24; P=0.04) as an independent predictor of appropriate ICD therapy for VT/VF at follow up. About one quarter of the patients received inappropriate ICD shocks during follow-up. These were often due to exercise- related arrhythmic events (including sinus tachycardia, atrial fibrillation and oversensing). A very large group, 21 (35%) patients, experienced lead-related adverse events at follow up. The present study represented the largest single center experience with ICD therapy in ARVD patients to date and highlighted the beneficial role of ICD therapy.

Roguin et al assessed the outcome of 42 ARVD patients treated with an ICD over 42 $\pm$ 26 months. Syncope and cardiac arrest were the main indications for ICD, and 33 (78%) patients received a median of 4 appropriate ICD interventions. Both clinical and laboratory predictors of appropriate ICD firings were identified: 1) induction of VT during programmed stimulation, 2) detection of spontaneous nonsustained VT on ECG, Holter or exercise treadmill testing, 3) moderate to severe RV dilation compared to no dilation, and 4) male gender.

ICD versus Pharmacological Therapy

Most of the published data regarding the efficacy of ICD therapy in ARVD patients have examined patients taking concurrent pharmacological therapy. However, often these patients received an ICD after failure of prevention of arrhythmic events by antiarrhythmic drug therapy, underscoring the importance of the ICD. Evidence for the efficacy of pharmacological agents has largely been anecdotal and generally the indication for drug therapy is to alleviate symptoms such as extrasystoles and recurrent palpitations. There are absolutely no randomized comparisons of drug and device therapy in the ARVD population.

Risk Stratification for ICD Therapy

The role of the ICD as a prophylactic measure to prevent SCD in patients who have not experienced a life-threatening even has not been tested in ARVD, in part because of poorly defined risk factors and the inability to identify the larger population at risk. Serious ventricular arrhythmias are often the first manifestation of the ARVD condition.

There is a strong trend toward implanting ICD in symptomatic ARVD patients, exemplified by aborted cardiac arrest, arrhythmogenic syncope, and sustained VT. A number of risk factors, such as male gender, spontaneous VT, moderate to severe RV dilation and VT during programmed stimulation have been used to identify those who will receive an ICD but it is premature to employ these variables as an indication of who should or should not receive ICD therapy. Further prospective investigative work will be needed to test the value of screening variables.

ICD Complications

As with any invasive therapy, ICD therapy brings with it certain inherent risks. Complications may occur at a higher rate in the ARVD patient due to adipose infiltration and replacement of the RV myocardium. These risks include RV perforation stemming from an extremely fragile RV wall, poor R wave amplitudes or high pacing thresholds resulting in difficult lead placement, extensive disease progression resulting in undersensing or failure to pace, and a failure to terminate ventricular arrhythmic events due to rising defibrillation thresholds over time.

Conclusion

Accepted indications for ICD therapy in ARVD include secondary prevention after cardiac arrest and/or sustained VT; the ICD is not yet used for primary prevention in asymptomatic ARVD patients or relatives with a high-risk profile. The decision to implant an ICD must be based on individual risk assessment, physician judgment and patient preference. Long term studies are promising in the development of risk stratification and will greatly facilitate this decision. Based on published data the ICD is a feasible and effective therapy for the prevention of SCD in the setting of ARVD.

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