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Review Article

Management of Ventricular Arrhythmias in ARVC Patients

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Abstract

Arrhythmogenic right ventricular cardiomyopathy is a genetically determined disease presenting primarily as an arrhythmia syndrome and ventricular dysfunction. It predominantly affects the right ventricle although left ventricular involvement is not uncommon, especially during later stages of the disease. Sudden cardiac death and ventricular arrhythmias are frequent presentations. Management of ventricular arrhythmias can be particularly challenging in these patients. Here we discuss the various strategies of arrhythmia management with particular emphasis on the emerging role of catheter ablation as a successful alternative to antiarrhythmic medications.

Keywords: *Ventricular Arrhythmias; Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)*

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined disease of the cardiac myocytes which in most cases primarily affects the right ventricle and in advanced cases the left ventricle as well. Predominant left ventricular disease has also been described. ARVC patients are typically susceptible to ventricular arrhythmias and sudden cardiac death (SCD) [1]. The propensity for ventricular arrhythmias, however, is usually out of proportion to the severity of functional impairment of the ventricles. The sine qua non of the disease is replacement of cardiac myocytes by fibrofatty tissue resulting in non-homogeneous tissue architecture which creates a substrate conducive for re-entrant ventricular arrhythmias [2]. Predisposition to sudden death in the very early stages of the disease before any morphological changes are obvious is not well understood.

Pathology and genetics

Although the exact pathological mechanism leading to fibrofatty changes is yet to be clearly elucidated, the disease in most cases has been linked to disruption of the structural function of desmosomal proteins. Cardiac desmosomes are found in the intercalated discs of the myocytes and are of vital importance in maintaining the structural integrity of the heart by anchoring the intermediate filaments of adjacent myocytes to the cytoplasmic membrane [3]. Majority of the mutations discovered so far, whether inherited or de-novo, encode for desmosomal proteins mainly plakophillin-2, desmoglein-2 and desmoplakin [4]. Mutational changes in desmosomal proteins are believed to result in their nuclear translocation leading to changes in intracellular signaling pathways with ultimate phenotypic expression resulting in cardiac fibrosis, adipocyte accumulation and ventricular arrhythmias [5]. In about 30% to 50% of the cases the disease is familial and is inherited in an autosomal dominant pattern with incomplete penetrance. A "triangle of dysplasia" has been described which includes the peritricuspid area, the infundibulum and the RV apex as the main regions of pathology [2]. The septum is less often involved. In the left ventricle the posteroseptal and posterolateral regions are most commonly affected [6]. The morphological changes first appear in the subepicardium and then proceed inwards towards the subendocardium [7].

Clinical presentation and diagnosis

Patients with early ARVC although at risk for SCD are generally asymptomatic and may only have minor ventricular arrhythmias and lack any obvious structural abnormalities on imaging. Patients typically present as young adults with symptomatic ventricular arrhythmias and over a period of time may go on to develop right ventricular failure and eventually biventricular failure. The rate of progression from one phase to another, however, is quite variable. At present there is no gold standard for diagnosis of ARVD and clinical diagnosis relies on modified Task Force criteria proposed in 2010 [8]. These criteria utilize imaging abnormalities, ECG findings, family history and histopathology for diagnosis. The original Task Force criteria proposed in 1994 although quite specific lacked sensitivity for recognition of early disease. The sensitivity was improved upon by the modified criteria while maintaining the specificity of the original criteria.

Risk of sudden death and ICD therapy

The annual risk of sudden cardiac death in clinical studies varies quite widely and is reported to be in the range of 0.08% to 3.9%. Based on available studies it is reasonable to conclude that ICDs are of clear benefit to survivors of SCD [9,10]. No large scale prospective studies have been conducted to assess risk markers for sudden death in ARVD patients. Clinical data and retrospective studies indicate that unstable ventricular arrhythmias and unexplained syncope are associated with up to 9% annual incidence of appropriate ICD therapy and, therefore, represent appropriate indications for ICD implantation for primary prevention [11,12]. Other markers shown to be independently associated in observational studies include QT dispersion, extent of T-wave abnormalities, extent of electro-anatomic scar and late potentials, presence of RV and LV dysfunction, degree of physical activity, high PVC burden, non-sustained VT and possibly certain genotypes. Family history of sudden cardiac death does not appear to increase the risk in the affected individual [12].

Antiarrhythmics

The overall efficacy of anti-arrhythmic medications for controlling symptomatic ventricular arrhythmias in ARVD is poor and their use in general is increasingly limited to decreasing the VT burden in patients with ICDs and those with recurrent VT despite catheter ablation. There are no prospective studies evaluating their role in primary prevention. For a long time sotalol was considered the anti-arrhythmic drug of choice for management of ventricular arrhythmias in ARVD, based on a study which assessed VT suppression in the electrophysiology lab [13]. Subsequently, data from the North American ARVC Registry, which followed patients in a prospective manner, indicated that amiodarone was the only effective agent, while sotalol appeared to be ineffective and in fact showed a trend towards pro-arrhythmia. Beta-blockers were shown to be neither harmful nor effective [14].

Catheter ablation

Catheter ablation is usually reserved for patients who have failed antiarrhythmic medications and those presenting with a VT storm. Over the years ablation for VT in ARVD has evolved from an endocardial only approach to a combined endo-epi procedure in most cases. Advances in mapping and catheter technology, and eventual incorporation of epicardial ablation has led to a gradual improvement in reported outcomes.

In ARVD patients patchy distribution of fibrofatty tissue interspersed with normal myocytes creates anatomic boundaries and corridors of slow conduction which provides a perfect electrical substrate for re-entry. Improvements in various technical aspects of VT ablation now allows detailed mapping of the endo and epicardial scar, as well as potential channels for VT circuits. An interesting observation has been that the change from dense scar to normal tissue in ARVD is abrupt and lacks the gradual transitional scar border zone seen in ischemic cardiomyopathy [15]. Also of interest is that abnormal late potentials may sometimes be seen in areas of normal voltage. Patients typically have multiple inducible monomorphic VTs of LBBB morphology and occasionally of RBBB morphology as well, especially when the left ventricle is affected. VT circuits are usually located in the peritricuspid region of the right ventricle [5,16].

Most clinical studies describing catheter ablation for ARVC are single center studies and are limited by inclusion of only a small number of patients given the low prevalence of the disease. Fontaine., *et al.* in 1989 were the first to describe the feasibility of catheter ablation in

ARVC patients; initially using DC shock energy (fulguration) and later radiofrequency ablation. Recurrent VT requiring repeat procedures, however, was common [17-19]. Two other groups, Ellison., *et al.* (1998) and Reithman., *et al.* (2003) reported outcomes of catheter ablation in a small series of patients (5 each). They achieved reasonable short term success although anti-arrhythmics were continued in the majority of patients following the ablation procedure [20,21].

Marchlinski., *et al.* in 2004 were the first to report consistent use of electroanatomical mapping for VT ablation in a relatively large series of ARVC patients. Their VT recurrence rate was 11% at 27 +/- 22 months of follow up. Acute procedural success was good with about 74% patients having no inducible VT at the end of the procedure. However, about 62% patients required more than one ablation procedure during follow up. Anti-arrhythmic medication use following the ablation procedure was not reported [22]. Verma., *et al.* (2005), also using electro-anatomic mapping, reported their single center experience in 21 patients. At one, two and three years of follow up their success rates were 77%, 73% and 53% respectively. Again, acute procedural success was good and VT remained inducible in only 18% patients. The study differed from prior ones in that ablation was purely substrate based and no attempt was made to map during VT. All patients, however, were continued on their anti-arrhythmic medications following the ablation procedure [15]. Dalal., *et al.* (2007) reported outcomes of a multi-center study in 24 ARVC patients who underwent a total of 48 RFA procedures. They reported a 14-month single procedure VT free survival of only 25%. Anti-arrhythmic therapy had to be resumed in 25% of the patients following the first procedure. However, only 10 procedures utilized an electro-anatomic mapping system, while the rest used conventional mapping techniques. Acute procedural success was also not satisfactory in that some form of VT (clinical or non-clinical) remained inducible in 54% of the patients at the end of the procedure [23].

Garcia., *et al.* (2009) were the first to report the use of epicardial ablation in ARVC patients. Epicardial mapping and ablation was performed in addition to endocardial ablation in a series of 13 patients. All patients had failed one or more prior attempts at endocardial only ablation. At the end of the procedure 85% of patients had no inducible VT and during 18 +/- 13 months of follow up, 77% patients had no VT recurrence. Only 3 patients were on antiarrhythmics at follow up including one for atrial arrhythmias with none being on amiodarone. They observed the size of the epicardial scar to be significantly larger than the endocardial scar. Uniform presence of multicomponent and late electrograms was an impressive feature on the epicardium. VT circuits were often noted in locations on the epicardium where there was no scar immediately opposite on the endocardium [5].

Bai., *et al.* in 2011 published a non-randomized prospective multi-center study comparing outcomes of endocardial only versus endo-epi ablation in 49 patients. They observed a statistically significant difference in VT-free survival at 3 years in patients undergoing endo-epi ablation versus endocardial only ablation (84.6 vs 52.2%). At follow up, majority of the patients (69.2%) were off anti-arrhythmic drugs in the group undergoing endo-epi ablation while only 21% were off anti-arrhythmics in the endo only group. One interesting observation made in their study was that frequent PVCs at the end of the ablation procedure were predictive of VT recurrence in the future [24].

The largest cohort of ARVC patients undergoing catheter ablation for VT was published by Phillips., *et al.* in 2012. Their study population of 87 patient spanned a period of 19 years and underwent ablation at multiple centers in the US and Canada. They reported freedom from VT as 47%, 21%, and 15%, at 1, 5, and 10 years, respectively. Epicardial ablation was performed in only 23 patients and cumulative freedom from VT following epicardial ablation was 64% and 45% at 1 and 5 years, respectively, which was significantly better than endocardial RFA. Although recurrences were fairly common in this study it is important to note that overall this was a heterogeneous patient population in terms of VT ablation technique, use of electroanatomic mapping and type of ablation catheter used [25].

A comparison of endo-epi vs epicardial only ablation strategies in a series of 30 patients was published by Philips and colleagues in 2015. They were able to achieve a 70% success rate at 2 years of follow up. There was no difference in recurrence rates of endo-epi ablation compared to epicardial only ablation. Even in patients who had a recurrence the VT burden was significantly reduced. All patients had a significantly larger epicardial substrate as previously demonstrated in other studies and the majority (69%) of the critical VT circuits were epicardial in location in the sub-tricuspid region. Also, majority of VT recurrences occurred during the first year after RFA, had fast cycle lengths, and required ICD shock for termination [26].

A study including a large series of patients undergoing catheter ablation for VT in ARVD patients was published recently by Santangeli., *et al* (2015). This single center study evaluated 63 patients undergoing endocardial only ablation as the initial procedure. Where endo-

cardial ablation was deemed to have failed adjuvant epicardial ablation was performed. Recurrence after endocardial only ablation (13 patients) or persistent inducibility at the end of endocardial ablation was considered a failure and led to additional epicardial ablation. Eventually epicardial ablation was performed in 63% of the patients. A total of 121 RFA procedures were performed in the 63 patients with 45% patients requiring only a single procedure. During a follow-up of 56 ± 44 months, VT-free survival was 71% with only a single VT episode observed in an additional 9 patients (15%). At follow-up, 64% patients were not on any anti-arrhythmic drugs and almost half of the remainder were on anti-arrhythmics for atrial arrhythmias. None of the patients were on amiodarone. Extensive areas of electroanatomic substrate were noted in the perivalvular regions (peritricuspid and RV infundibulum) but surprisingly none in the region of the RV apex as previously reported. The authors concluded that endocardial only strategy may be effective in selected cases and should always be pursued as the initial ablation strategy. They also suggested that comprehensive endocardial ablation of the perivalvular substrate is important because this area may not be adequately addressed epicardially due to proximity to major coronary vessels and presence of fat [27].

One interesting study published in 2013 by Phillips., *et al.* demonstrated that there was a high prevalence of catecholamine facilitated focal VT originating from the scar border zone in ARVC patients which correlated with their clinical PVCs of similar morphology. Ablation of these foci in addition to ablation of scar related arrhythmia resulted in 85.2% and 74.5% cumulative freedom from VT at 1 and 2 years, respectively [28].

Conclusion

To summarize, management of patients presenting with symptomatic ventricular arrhythmias requires an approach incorporating multiple therapeutic modalities. Of initial concern is risk stratification for prevention of sudden cardiac death. This remains a controversial field although there is reasonable evidence to support the fact that patients presenting with unstable ventricular arrhythmias and unexplained syncope should receive an ICD. Although anti-arrhythmic drug use for suppression of ventricular arrhythmias remains an important cornerstone of therapy in symptomatic patients, their long term use is of uncertain benefit. Amiodarone has been shown to be the only effective agent for ARVC but its prolonged use in young patients is problematic given its wide range of serious adverse effects. In recent years, catheter ablation has emerged as a feasible option for control of ventricular arrhythmias in ARVC patients. Although studies evaluating the efficacy of catheter ablation are small single center experiences and usually retrospective in design, they have consistently demonstrated an ability to either completely eliminate monomorphic ventricular tachycardia or result in a significant decrease in ventricular arrhythmia burden. This is especially true of the more recent studies where advances in understanding of the underlying substrate has led to frequent use epicardial mapping and ablation with resultant improvements in short and long term procedural success. These results are not unexpected given the underlying arrhythmia substrate is quite amenable to current catheter based ablation techniques. Successful ablation has allowed these patients to come off their anti-arrhythmic medications and even when ablation is unable to completely eliminate the arrhythmia it can result in decreased utilization of ICD therapies which can markedly improve the quality of life for these patients. Complications related to these procedures have been acceptably few. Pulmonary embolism has been reported as one of the unusual complications [27]. This is not surprising given these patients are susceptible to thrombus formation within a dilated and hypocontractile right ventricle. Use of aggressive anticoagulation for a short period post-procedure, therefore, seems a reasonable strategy to minimize the risk of this complication. A significant proportion of patients undergoing ablation do seem to require more than one procedure over long term follow-up, perhaps partly because of the changing substrate. Repeated ablations may possibly be required over time in ARVC patients as the disease evolves. It is important to realize that elimination of the clinical VT may not be an adequate procedural end-point for ARVC patients. Studies demonstrating good outcomes have focused on comprehensive modification of the anatomic and electric substrate in addition to elimination of the presumed clinical tachycardia. This strategy is important given the clinical VT represents only one of the many potential arrhythmias in the presence of an extensive and evolving substrate. One study also demonstrated that focal catecholamine induced VT may be frequent in patients with ARVC and partly responsible for some of the recurrences. This makes mechanistic sense since most VT in ARVC is exercise induced and recurrent VT post ablation has shown to be have fast cycle lengths requiring ICD shock and

predicted in some cases by the patient's by the PVC burden following ablation [24,26]. As mapping and ablation technology continues to improve, and as we gain a better understanding of this arrhythmic substrate based largely in anatomic heterogeneity, it is likely that the role of catheter ablation will continue to expand and result in improved outcomes in the future.

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