

The role of anti-arrhythmic drugs and ablation in arrhythmogenic right ventricular cardiomyopathy

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Abstract

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a disease characterized by fibrofatty replacement of the ventricular myocardium, leading to ventricular arrhythmias and sudden cardiac death. Treating this condition can be challenging due to progressive fibrosis, phenotypic variations and small patient cohorts limiting the feasibility of conducting meaningful clinical trials. Although widely used, the evidence base for anti-arrhythmic drugs is limited. Beta-blockers are theoretically sound, yet their efficacy in reducing arrhythmic risk is not robust. Additionally, the impact of sotalol and amiodarone is inconsistent with studies reporting contradictory results. Emerging evidence suggests that combining flecainide and bisoprolol may be efficacious.

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Radiofrequency ablation has shown some potential in disrupting ventricular tachycardia circuits, with endo/epicardial ablation yielding better results when done jointly, possibly as an index procedure. In addition, stereotactic radiotherapy may be a future option that can decrease arrhythmias beyond simple scar formation by altering levels of Nav 1.5, Cx 43, and Wnt signaling, potentially modifying myocardial fibrosis.

Future therapies, such as adenoviruses and GSk3b modulation, are still in early-stage research. While implantable cardioverter-defibrillator (ICD) implantation is the key mechanism for reducing arrhythmic death, the risks of inappropriate shocks and device complications must be carefully considered.

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Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a form of Arrhythmogenic Cardiomyopathy characterized by fibro-fatty replacement of the myocardium. There is a spectrum of disease which primarily affects the right ventricle (RV)-termed "Arrhythmogenic Right Ventricular Cardiomyopathy" but left ventricular and biventricular forms exist. The primary presentation can be sudden cardiac death¹.

Mutations in desmosomal proteins are present in the majority of probands but there are a significant proportion of gene elusive cases. Desmosomes are complex structures that form at the intercalated disc (ID) comprising of cadherins, armadillo proteins and intermediate filaments. They provide structural support and facilitate cell-cell signalling. Mutations in these proteins lead to fibrofatty replacement of the RV, and, less commonly the left ventricle, resulting in a proarrhythmic state². Non-desmosomal proteins such as TMEM43 and phospholamban are associated with ARVC, occur less frequently than desmosomal mutations and can be more aggressive³.

The diagnosis of ARVC can be challenging, being based on Task Force Criteria and has been discussed extensively in this journal previously⁴. This review will focus on the treatment of ventricular arrhythmias (VA) in ARVC which is comprised of anti-arrhythmic drugs (AADs), implantable cardioverter defibrillators (ICDs) and radiofrequency ablation (RFA).

Arrhythmias in ARVC

VAs commonly cause morbidity and mortality in ARVC. Desmosomal mutations disrupt the complex cellular architecture and signaling pathways within cardiomyocytes leading to conduction velocity (CV) slowing, prolongation of conduction pathways, heterogeneities in CV, action potential duration and thus lethal re-entrant VAs (figure 1).

CV is partly determined by the source:sink relationship whereby the "source" relates to the depolarizing power of a unit of cells and the "sink" relates to tissue that is depolarized⁵. Decreasing the size of the source or increasing the size of the sink decreases CV. The strength of the source is governed predominantly by the availability of active sodium channels which are reduced in acute ischemia⁶, heart failure⁷ and ARVC⁸.

In addition to conduction slowing, prolonged conduction pathways due to source:sink mismatch can be proarrhythmic. This is especially relevant adjacent to scar tissue where large areas of relatively normal tissue are connected to small conduction pathways within the scar tissue⁹.

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Nav1.5 channels predominate at the JD in the same protein complex as the desmosomal protein-plakophilin⁸. Cellular studies of plakophilin 2 (PKP2) gene knock out mice have demonstrated a reduction in Nav1.5 channels, altered sodium current and reduced CV⁸. Additionally, immunohistochemistry labelling of ARVC cardiac biopsies have shown decreased levels of Nav1.5 channels at the JD¹⁰. PKP2 mutations appear to cause reduction of CV by reducing the number of available Na channels thereby contributing to arrhythmia formation.

Gap junctions are another key determinant of CV. These are intercellular channels present at the JD and allow for depolarisation to spread from cell-cell⁵. Connexin43 levels are reduced in animal models and myocardial biopsy samples from patients with ARVC^{10,11}. The above data suggest that desmosomal mutations, Nav1.5 channels and connexin43 expression are all inherently linked in the pathogenic formation of arrhythmias in ARVC. This may be due to impairment of microtubules that organise and deliver these components to the JD¹².

Altered calcium handling occurs in proarrhythmic disease states including ARVC¹¹. Murine ARVC models demonstrate altered calcium handling alongside increased frequency and duration of calcium spark events¹³. This could be a cause of the increased ventricular ectopic (VE) burden in ARVC which is associated with the increased risk of VAs¹⁴.

Abnormal calcium release at various points within the action potential can lead to early-after depolarisations which if not large enough to trigger an action potential can lengthen the action potential locally¹⁵. This heterogeneity of action potential duration is well documented as being proarrhythmic in other diseases, though has not yet been investigated in ARVC.

The hallmark histological finding of ARVC is fibrofatty replacement of myocardium due to altered transcription factor signalling via the Wnt beta catenin pathway triggered by defective plakoglobin^{16,17}. The relationship between scar and VT has been well studied in myocardial infarction where strands of surviving myocardium penetrate through scar zones creating pathways where conduction can pass slowly¹⁸. These form circuits in the border zones between healthy myocardium and dense scar allowing re-entrant arrhythmias to propagate. Re-entrant VT a key mechanism of arrhythmia in ARVC and regions of diffuse fibrosis capable of supporting re-entry represent the main target for ablation.

TREATMENTS

Risk Stratification

Risk stratification is critical in managing ARVC, where VA is a major cause of death. While ICDs are recommended for secondary prevention, the optimal approach for primary prevention remains unclear. An ARVC risk calculator was created by following ARVC patients longitudinally across 14

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academic centres in six countries. Utilising the data, a model was created using weighted risk factors to predict the risk of VAs, potentially reducing ICD implants by 20% while protecting 89.9% of patients with VA¹⁹. The risk score did not include genotype, a key determinant of phenotype²⁰. A subsequent study found that risk scores for certain genotypes, like PKP mutations, were predicted more accurately than gene-elusive cases. Additionally, the weight of certain risk predictors varied between genotypes. This emphasises the need for genotype to be incorporated into newer risk scores to improve accuracy. An important limitation of the score is that while they generate a specific risk percentage of VA, they do not provide a clear cut off for when an ICD should be implanted. Therefore, the decision to implant an ICD should be individualized, taking into account the patient's overall clinical status, risk score and preference.

Exercise in ARVC

Exercise increases disease progression and arrhythmic risk in ARVC as demonstrated in animal models and retrospective cohort studies. Strenuous exercise is associated with increased risk of life-threatening arrhythmias²¹. There is evidence of a dose response linking the burden of exercise in ARVC and rate of disease progression, with endurance athletes developing the most rapid rates of disease development²². Exercise reduction after diagnosis of ARVC has been associated with lower arrhythmic risk but does not do so enough to warrant precluding ICD implantation²³. Exercise reduction provides a simple treatment in a disease where suppression of VAs can be challenging.

Anti-arrhythmic therapy in ARVC

Beta blockers

Beta blockers are frequently used in ARVC²⁴, however, their efficacy is unclear. [NO PRINTED FORM]

A recent registry study suggested that bisoprolol reduced the composite of sudden cardiac death or major VAs, only with doses greater than 5mg²⁵.

In patients with known VT inducibility, beta blockers failed to suppress VT inducibility in 0 out of 7 patients in a VT stimulation protocol²³ while in another cohort where VT was known to be non-inducible, beta blockers decreased the presence of ventricular runs in only 2 out of 7 patients²⁶.

A North American Registry assessed the efficacy of AADs in patients with ICDs and found that beta blockers had no impact on VAs or ICD therapies in 58 patients²⁷. Subgroup analysis showed those

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taking atenolol had a reduced risk of clinically relevant arrhythmias but this may be due to confounding variables including physician choice.

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Theforementioned suggest the use of beta blockers is not fully proven to be beneficial. This could be due to the absence of randomized clinical trials, retrospective registry data and heterogeneous cohorts of patients at different stages of disease progression. For now, beta blockers provide an AAD with minimal side effects, and are recommended in international guidelines²⁴.

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Sotalol

Sotalol inhibits potassium channels and has limited class 2 effects²⁸. Using VT stimulation studies, Wichter found sotalol was the most effective AAD rendering VT non-inducible in 22 out of 38 patients. In non-inducible cases, it provided complete suppression in 23 out of 35 patients²⁶. These are promising results, however registry data is less optimistic.

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Cappelletto et al found sotalol to have no effect on their cohort²⁵ while Marcus et al demonstrate starkly contrasting results from their North American registry data suggesting patients taking sotalol (n=38) were at increased risk of clinically relevant VAs and ICD therapies²⁷. The different findings compared to Wichter's study may be related to improved detection of VT, or a more advanced disease cohort of patients – i.e. those with ICDs.

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Due to the disparate findings and potential for causing harm, sotalol's usage cannot be fully advocated and is not mentioned in taskforce guidelines.

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Amiodarone

Amiodarone inhibits inward rectifier potassium channels—a class 3 effect of uniformly increasing refractory periods though also has class 2, 3 and 4 effects. The data on it's impact on life threatening arrhythmia is variable. A number of registry studies report no impact^{25,26}. Marcus et al state their 10 patients taking amiodarone had a significantly lower risk of developing life threatening VAs alongside a reduced time to first arrhythmia²⁷.

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This disparity may be due to low patient numbers, different disease stages and inherent bias. AADs are often changed between patients by the clinician for a variety of reasons and drawing an accurate comparison between such patients and those not on AADs becomes difficult.

The use of amiodarone in the young cohort of ARVC patients remains challenging without overt evidence of its efficacy and long-term side-effects. Amiodarone usage is limited to expert use on a case-by-case basis²⁴.

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Flecainide

This class 1c [AAD](#) inhibits Nav1.5 sodium channels, slowing the action potential upstroke and prolonging the refractory period. Additionally, it inhibits ryanodine receptor opening preventing calcium release which is the likely mechanism of beneficial action in catecholaminergic polymorphic VT²⁹. It is efficacious in a murine PKP2 model¹³.

There is some promise for its role in ARVC when combined with beta blockers: a case series demonstrates a reduction in [VAs](#) in [these patients](#)³⁰. A larger retrospective study showed a reduction in [VEs](#) and inducibility of [VT](#)³¹.

These data provide some promise for combination of beta blockers and flecainide-this is supported by long term follow-up of patients on combination therapy over 5 years with a 5% VA event rate at 1 year, 25% at 5 years and no deaths.

Radiofrequency Catheter Ablation in ARVC

Given the relative inefficacy of drug therapy for the prevention of [VAs](#), [RFA](#) presents itself as an alternative and is recommended for recurrent VT cases despite maximal pharmacological therapy²⁴. Unfortunately, it is not a panacea and although complication rates are low, freedom from arrhythmia over time is modest at best, owing to the progressive nature of [ARVC](#)³².

As discussed previously, a complex proarrhythmic phenotype develops in patients with ARVC in regions of fibro-fatty replacement which create optimal conditions for re-entry. These regions can be targeted with [RFA](#) destroying the anatomical circuit, terminating the VT and theoretically preventing its recurrence, albeit for a period of time. Importantly, since ARVC begins as an epicardial process this often requires epicardial ablation. Major advances in mapping catheter technology with high density grids using small closely spaced electrodes mean that very discrete circuits and pro-arrhythmic sites can be identified. Indeed, there has been a recent focus on substrate-based ablation targeting channels within scarred regions that can support re-entry in the myocardium. This allows ablation in sinus rhythm with confirmation of the region's importance during VT induction by identifying if the site is part of the critical isthmus in the diastolic pathway of the VT circuit (figures 2 &3). Such an approach avoids prolonged periods of mapping a circuit whilst the patient is in a hemodynamically unstable VT although there is ongoing debate regarding identification of optimal targets in sinus

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rhythm whether these are electrophysiological or imaging based e.g. border of an RV aneurysm, sites of wall thinning.

The combination of sophisticated mapping systems and irrigated radiofrequency catheters enable precise targeting of the circuits. This has been progressed further by safer techniques to access the epicardium and facilitate epicardial ablation. However, scar can be intramural requiring additional ablation both endo and epicardially, bipolar energy or ethanol delivery. Indeed MRI is being increasingly used to delineate regions of scar to target mapping and ablation, especially for intramural substrates with advances in software to delineate channels that could support VT (figure 4 &5).

Romero et al recently conducted a meta-analysis comparing the efficacy of epicardial and endocardial approaches in 9 trials. VT recurrence was 49.6% in the endocardial and 26.4% in the endo-epicardial group³² translating into a clinically significant 42% relative risk reduction and 23% absolute risk reduction in VT recurrence. There was no difference in all-cause mortality. The meta-analysis didn't account for differences in techniques between studies or if endo-epicardial ablations were staged or part of one procedure.

Interestingly, no differences were seen between approaches in the ability to induce VT at the end of the procedure. This may be explained by endocardial ablation eliminating enough of the VT circuit to terminate the arrhythmia at the time of ablation, but leaving enough epicardial substrate to allow VT to recur as new scar forms. Lin et al demonstrated in their cohort that VT originated from areas corresponding to progressive scar, calculated based on voltage mapping, 72.9% of the time in patients undergoing repeat ablation³³.

Guidelines recommend epicardial ablation only if an endocardial approach has failed, however combining the approaches in one procedure may allow more complete treatment in one procedure²⁴. Risk of adverse effects may contribute to apprehension towards a combined approach with cardiac tamponade being particularly feared. Romero et al's meta-analysis showed no difference in major procedural complications with epi-endocardial ablation³² however another meta-analysis contradicted this³⁴. This could be due to type 1 error as trial sequential analysis indicated possibility of a false positive result in the latter. Another group reported only one procedural complication of a delayed reactive pericardial effusion from a combined approach in 166 procedures³⁵. Multiple procedures appear to yield improved results with freedom from VT for 81.8%, 76.8% and 69.6% of patients at 1, 2 and 5 years.

Stereotactic Radiotherapy – Could this be used in ARVC?

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Stereotactic radiotherapy (SR) has recently been translated from oncological targets into treating

[VA](#)³⁶

Initial case series demonstrate the efficacy of delivering focused radiation to areas of scar identified by imaging and non-invasive ECG Imaging techniques reducing arrhythmia burden³⁷. This is often in cohorts of patients where AADS and [RFA](#) have either been contra-indicated or unsuccessful.

The ENCORE-VT phase I/II trial targeted areas of scar in patients with ischaemic and non-ischaemic cardiomyopathy with SR³⁸. This demonstrated a 94% reduction in VT episodes across the entire cohort and an associated reduction in anti-tachycardia pacing ([ATP](#)) and ICD therapies over a median follow up time of 13 months. 28% of patients developed pericardial effusions and 10% developed radiation pneumonitis which resolved with the administration of oral steroids. Adverse effects notwithstanding, these are impressive results in a cohort of patients with advanced disease refractory to current treatments. Similar results have been demonstrated in other cohort studies and phase I/II clinical trials^{39,40}. These now need to be validated in multicentre studies with long term safety data to detect delayed effects.

The initial mechanism of success was thought to be apoptosis and fibrosis. The expectation being that critical isthmi would be converted to fibrotic non-conducting tissue. [However, VT suppression was observed before the onset of fibrosis suggesting alternative mechanisms](#)⁴¹.

Histological and animal studies have shown that mechanisms include increases in Nav1.5 channel & Cx43 expression and increased notch signalling affecting Wnt signalling and fibrofatty formation⁴². [These effects appear to target pathophysiological mechanisms seen in ARVC, and additional studies are required to assess this.](#)

Internal Cardiac Defibrillators (ICD's)

ICDs provide the main protection against arrhythmic sudden death in ARVC. The largest study of 132 patients showed an actual survival rate of 96%: 24% of patients would have died without an ICD due to VF⁴³. These findings have been reproduced in other studies⁴³.

However, the risk of complications is not insignificant with inappropriate shocks and lead failures comprising the majority of these. A meta-analysis examining complications in ICDs in patients with inherited cardiomyopathies found [an annual risk](#) 3.9% risk of inappropriate shocks [and](#) 4.2% [for](#) of [device complications](#) with the most common being lead malfunction or lead dislodgement occurring in 12 and 4.3 percent of patients respectively⁴⁴. There is some evidence that isolated ablation in ARVC

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patients without an ICD can be utilised if the ablation results in non-inducible VT-in a series of 32 [patients](#) who declined/refused an ICD there were no deaths on 3 year follow-up⁴⁵

Subcutaneous ICDs (S-ICDs) minimise lead complications but [currently lack ATP capability](#). In ARVC, they have been associated with a 4.5% risk of inappropriate shocks predominantly due to oversensing extra-cardiac signals which is comparable to transvenous systems. [There are no long-term data to assess whether changes in ECG morphology due to disease progression \(e.g. development of RBBB, loss of R wave amplitude\) increases](#) inappropriate shock rates⁴⁶. No head-to-head trials have been undertaken and registry data are not randomised. However, this device offers a promising alternative to ARVC gene carriers at risk of cardiac arrest or those wishing to avoid transvenous leads. The evolution of leadless pacemakers to combine with [S-ICDs](#) may create an avenue to deliver [ATP](#) if required.

ICD therapy remains vital in [treating](#) ARVC and unlike AADs has strong clinical evidence supporting its use.

Future Therapies

Gene mutation based therapeutic targeting remains an active area of research. Myocardial gene therapy relies on the use of adenoviruses with an affinity for human myocardium. [It has a number of challenges](#) including requirement of high levels of transcription, the presence of neutralising antibodies and [duration of effect](#)⁴⁷. Further research is required in addressing these issues prior to it being utilised broadly in cardiovascular disease.

Other potential treatments avenues include preventing oxidative stress and damage to the nuclear envelope which has [been highlighted as](#) a potential mechanism of cell loss in ARVC. Upregulating SIRT3 by administering honokiol caused a reduction in reactive oxidant species [rescuing an ARVC](#) phenotype⁴⁸. This was in a cellular model and although it doesn't recreate the complex three-dimensional architecture of [ventricular myocardium](#) it provides potential therapeutic targets.

[Abnormalities in Wnt/beta catenin signalling pathways](#) increase adipogenic transcription factors and are [deemed](#) a key pathophysiological mechanism. [GSK3b inhibition](#), a tyrosine kinase [which](#) inhibits beta catenin, has been shown to reverse ARVC phenotypes⁴⁹. Although no human clinical trials have taken place in ARVC, GSK3B inhibition is the focus of numerous oncological clinical trials⁵⁰.

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Figure 1. Electrophysiological Factors predisposing to ventricular arrhythmias in ARVC

[Figure 2. Individual risk factors that combine to form the 2019 ARVC risk calculator.](#)

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CONCLUSION ¶

ARVC is a progressive and challenging disease associated with significant morbidity and mortality. Although widely used, the evidence base for AADs is limited. Catheter ... [1]

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Figure 3. Mapping of VT substrate in ARVC. A. Low voltage area in superior right ventricle epicardial surface (delineated by white outline). B. Paced extrasystoles (sensed extra beats) demonstrating late potentials (circled in yellow) in low voltage region indicative of a channel where VT developed during the VT stimulation protocol.

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Figure 4. Example of a mapping VT activation in ARVC. An epicardial VT circuit mapped with contact signals (A) and non-invasive ECG Imaging (B), illustrating continuous diastolic activation in VT. The deep red regions represent the site of earliest activation in the ventricle prior to the QRS complexes in VT which were the target of ablation.

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Figure 5. Representative cases of the two major phenotypes associated with Arrhythmogenic Cardiomyopathy. Case A is a patient in their 40's who presented with palpitations and breathlessness and was identified to carry the pathogenic variant p.Gln1511* in the DSP gene. The phenotype is characterised by severe reduction of the LV systolic function, increased burden of VE and non-sustained VT. Cardiac MRI revealed significant ring-like scarring that affects, circumferentially, the sub-epicardial and mid-wall layers of the myocardium. Case B is a patient in their twenties who has a family history of sudden cardiac death in their sibling and is presenting as part of routine family screening. They were found to carry the familial p.Ser615Phe variant in the PKP2 gene. The phenotype is characterised by predominant RV dilatation, reduced RV systolic function and regional wall motion abnormalities in the RV free wall. There is preserved LV systolic function and chamber size but with mild LV scarring at the inferolateral wall (shown in figure).

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Figure 6. A. Circumferential epicardial fibrosis on MRI in ARVC patient with recurrent VT highlighted by late gadolinium enhancement (yellow arrows) B. Corresponding epicardial voltage map showing low voltage areas (<0.1mV) in red and normal myocardium in purple. The patient had a normal endocardial map illustrating the epicardial location of the substrate in many patients with ARVC.

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