Implantable Cardioverter/Defibrillator Therapy in Arrhythmogenic Right Ventricular Cardiomyopathy

Single-Center Experience of Long-Term Follow-Up and Complications in 60 Patients

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Background—Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a major cause of ventricular tachycardia (VT) and cardiac arrest in young patients. We hypothesized that treatment with implantable cardioverter/defibrillators (ICDs) is safe and improves the long-term prognosis of ARVC patients at high risk of sudden death.

Methods and Results—Sixty patients with ARVC (aged 43±16 years) were treated with transvenous ICD systems. Despite a higher number of right ventricular sites tested for adequate lead positions (P<0.05), lower R-wave amplitudes (P<0.001) were achieved in ARVC patients compared with other entities. During follow-up of 80±43 months (396 patient-years), event-free survival was 49%, 30%, 26%, and 26% for appropriate ICD therapies and 79%, 64%, 59%, and 56% for potentially fatal VT (>240 bpm) after 1, 3, 5, and 7 years, respectively. Multivariate analysis identified extensive right ventricular dysfunction as an independent predictor of appropriate ICD discharge. Fifty-three adverse events occurred in 37 patients during the perioperative (n=10) or follow-up (n=43) period, mainly related to the leads (n=31 in 21 patients). No lead perforation was observed. Freedom from adverse events was 90%, 78%, 56%, and 42% and freedom from lead-related complications was 95%, 85%, 74%, and 63% after 1, 3, 5, and 7 years, respectively.

Conclusions—These results strongly suggest an improvement in long-term prognosis by ICD therapy in high-risk patients with ARVC. However, meticulous placement and long-term observation of transvenous lead performance with focus on sensing function are required for the prevention and/or early recognition of disease progression and lead-related morbidity during long-term follow-up of ICD therapy in ARVC. (Circulation. 2004;109:1503-1508.)

Key Words: cardiomyopathy • heart arrest • tachyarrhythmias • defibrillators, implantable • arrhythmogenic right ventricular dysplasia

A arrhythmogenic right ventricular cardiomyopathy (ARVC) is a myocardial disorder that frequently underlies ventricular tachycardia (VT) and sudden death in a young population. The morphological and arrhythmogenic substrate of ARVC predominantly affects the right ventricle (RV) and is characterized by progressive myocardial atrophy with subsequent replacement by fatty and fibrous tissue.

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Although used increasingly in prevention of sudden death and treatment of VT, the role of implantable cardioverter/defibrillators (ICDs) in ARVC has been addressed only in case reports and small series, including our own preliminary reports. On the basis of these early results, we hypothesized that in a high-risk subgroup of patients with ARVC, treatment with ICDs is safe and may improve long-term survival. However, concern has been expressed about the potential risks and complications of lead implantation in a diseased RV myocardium, including RV perforation and insufficient pacing and sensing function. Therefore, we report our single-center experience with regard to the long-term results of ICD therapy in 60 patients with ARVC.
### TABLE 1. Clinical Characteristics of 60 ARVC Patients Receiving an ICD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range)</td>
<td>43±16 (14–70)</td>
</tr>
<tr>
<td>Gender, n, male/female</td>
<td>49/11</td>
</tr>
<tr>
<td>NYHA functional class II/III, n (%)</td>
<td>34/19/7 (56/32/12)</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>66±±11</td>
</tr>
<tr>
<td>LV involvement, n (%)</td>
<td>19 (32)</td>
</tr>
<tr>
<td>Extensive ARVC, n (%)</td>
<td>31 (52)</td>
</tr>
<tr>
<td>Family history for ARVC, n (%)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>History of arrhythmias, n (%)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Survived cardiac arrest</td>
<td>20 (33)</td>
</tr>
<tr>
<td>Hemodynamically intolerable VT/VF</td>
<td>35 (58)</td>
</tr>
<tr>
<td>Syncope</td>
<td>17 (28)</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>54 (90)</td>
</tr>
<tr>
<td>Inducible VT/VF during PES</td>
<td>43 (72)</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; LV, left ventricular; EF, ejection fraction; and PES, programmed electrical stimulation.

### Methods

#### Patient Population

Between January 1991 and December 2002, 60 of 273 patients (22%) with ARVC received an endocardial ICD system at the University Hospital of Münster. Patients were consecutively enrolled and prospectively monitored. Follow-up started at the time of ICD implantation and ended at the last follow-up visit, heart transplantation, or death. Informed consent was obtained from all patients, and procedures were in accordance with institutional guidelines.

All patients were diagnosed with ARVC according to the criteria proposed by an international study group. Detailed diagnostic evaluation included ECG (12-lead resting and exercise), Holter, signal-averaged ECGs, 2D echocardiography, left and right ventriculography, coronary arteriography, and programmed ventricular stimulation in all patients, as reported earlier. Additional diagnostic workup included MRI (n=41) and endomyocardial biopsy (n=50).

The characteristics of the study population are summarized in Table 1. The patients (49 male, 11 female) had a mean age of 43±16 years (range, 14 to 70 years) at implantation. Thirty-one patients (52%) with severe regional (>2 RV areas) or global (RV ejection fraction ≤45%) RV dysfunction were classified as having extensive ARVC. Indications for ICD implantation were related to secondary prevention in 56 patients (93%) after episodes of resuscitated cardiac arrest (n=20), documented sustained VT (n=34), or syncope (n=2). Ventricular arrhythmias were hemodynamically unstable and potentially life threatening in 35 patients (58%) or refractory to antiarrhythmic drug therapy in 21 patients (35%). Four asymptomatic patients (7%) with ARVC received the ICD for primary prevention of sudden death because of inducible VT during electrophysiological study and a family history of cardiac arrest in first-degree relatives.

#### Devices and Intraoperative Testing

All patients received transvenous endocardial defibrillation leads. Additional subcutaneous (n=9 patch; n=6 array) or transvenous (n=6 superior vena cava) leads were implanted in 15 patients (25%), nearly all of them before biphasic defibrillation and active cans were available. Four patients (7%) received dual-chamber ICDs with an additional right atrial lead. After the leads were positioned, sensing, pacing, impedance, slew rate, and defibrillation threshold were assessed. Careful attention was paid to achieve adequate sensing results (>7 mV). All devices were able to store electrograms and/or RR intervals from the treated arrhythmia events.

#### Concomitant Antiarrhythmic Treatment

At the time of hospital discharge, 19 patients (32%) known to have frequent VT episodes received concomitant antiarrhythmic drugs, including amiodarone (n=2), sotalol (n=13), or class-1 drugs (n=4), to preclude frequent appropriate ICD therapies. Another 13 patients (22%) received β-blockers, mainly to prevent inappropriate ICD discharges due to paroxysmal atrial fibrillation or exercise-related sinus tachycardia. At the time of most recent follow-up, 29 patients (48%) received antiarrhythmic agents, including amiodarone (n=8), sotalol (n=17), class-1 drugs (n=2), or combinations (n=2; sotalol with class-1 drugs). In addition, 17 patients (28%) were treated with β-blockers.

### Evaluation of Events

After hospital discharge, follow-up visits were scheduled at 3-month intervals or in case of an adverse event. During these visits, ICD therapies and adverse events were assessed and subsequently analyzed and classified. Follow-up information was detailed and complete in all but 1 patient (98.3%), who was lost to follow-up 46 months after implantation.

#### ICD Therapies

An ICD therapy was classified as appropriate if the stored electrograms and/or RR intervals retrieved from the ICD confirmed that the tachyarrhythmia before the first treatment by the device was sustained and of ventricular origin. ICD discharges within the first week after ICD implantation were not included in the subsequent analysis.

In accordance with previous studies, nonfatal events included ventricular tachyarrhythmias of any rate and fast VT/ventricular fibrillation (VF), which was defined as >240 bpm. Hypothetical mortality curves were calculated by adding the recurrence rate of fast VT/VF to the all-cause mortality, assuming that ICD implantation would not prevent nonarrhythmic or noncardiac death. Benefit from ICD implantation on survival of life-threatening VT/VF was estimated by the difference between hypothetical death and all-cause mortality rates.

An inappropriate ICD therapy was defined as a device discharge for supraventricular tachycardia (ie, sinus tachycardia, atrial fibrillation with fast AV conduction), oversensing, or nonsustained VT.

#### Adverse Events

Complications of ICD therapy included perioperative events occurring within 30 days of implantation and adverse events during long-term follow-up. An adverse event was classified as severe in case of long-term sequelae, hospitalization, or surgical revision.

### Statistical Analysis

Data are expressed as mean±SD. Student t test was used for comparison of continuous variables. Differences between groups were assessed by 1-factorial ANOVA test. To account for variable lengths of follow-up, the probability of remaining event free was analyzed by the Kaplan-Meier method, and differences in event-free survival between groups were evaluated with the log-rank test. Multivariate analysis was performed with the use of Cox regression analysis and variables that were found statistically significant in univariate analyses. A probability value of <0.05 was considered statistically significant.

### Results

#### Intraoperative Testing

Compared with patients with other diseases receiving ICDs at our institution in the same period, more positions of the tip of the RV lead had to be tested until adequate sensing was achieved in patients with ARVC (P<0.05). This meticulous intraoperative testing resulted in appropriate defibrillation and pacing thresholds, which were comparable to those in patients with other diseases. However, the final R-wave amplitude achieved in ARVC remained lower (P<0.001) (Table 2).

In patients with extensive ARVC, testing of even more RV positions (4.5±3.7 versus 1.7±1.1; P<0.001) resulted in...
even lower R-wave sensing amplitudes (9.4±2.8 versus 11.6±2.6 mV; P<0.005) compared with localized ARVC despite the use of atypical lead positions (n=14) and/or an additional pace/sense lead (n=2) to secure adequate sensing results.

Deaths
There were no perioperative deaths. During follow-up of up to 12 years (mean, 80±43 months; range, 6 to 147 months) or 396 patient-years, 8 of 60 patients (13%) died suddenly (n=2) or because of intractable biventricular heart failure (n=2) or noncardiac causes (n=4). The overall survival rates were 100%, 94%, 94%, 87%, and 76% after 1, 3, 5, 7, and 10 years, respectively (Figure 1, Table 3).

Transplantation
Two patients with progressive and intractable right heart failure underwent successful cardiac transplantation 44 and 58 months after ICD implantation.

Appropriate ICD Therapies
During follow-up, 39 of 56 patients (70%) with a history of sustained VT/VF and/or syncope and 2 of 4 patients with a prophylactic indication for ICD implantation received appropriate ICD therapies by either cardioversion (n=2) or antitachycardia pacing only (n=10). The interval from ICD implantation to the first appropriate ICD therapy ranged from 0.3 to 41.4 months (median, 4.1 months). Survival free of appropriate ICD therapy was 49%, 30%, 26%, and 26% after 1, 3, 5, and 7 years of follow-up, respectively (Figure 1).

Multivariate analysis identified extensive RV dysfunction (odds ratio, 2.09; 95% CI, 1.03 to 4.24; P=0.041) as an independent predictor of appropriate ICD therapy during follow-up (Figure 2). Inducible VT/VF during electrophysiological study (odds ratio, 2.16; 95% CI, 0.94 to 5.0; P=0.069) and left ventricular involvement (odds ratio, 1.94; 95% CI, 0.93 to 4.05; P=0.078) showed a trend toward statistical significance in the multivariate model. Twenty-four patients (40%) had at least 1 episode of fast VT (>240 bpm), which was identified as ventricular flutter (n=10) or fibrillation (n=7) in 17 of them. Freedom from fast VT/VF recurrences was 79%, 64%, 59%, and 56% after 1, 3, 5, and 7 years (Figure 1). Inducible VF during electrophysiological study was the only clinical variable during univariate Cox regression analysis that was associated with fast VT/VF recurrences during follow-up. The estimated benefit of ICD implantation in preventing potentially fatal events13,14 was 21%, 32%, 36%, and 35% after 1, 3, 5, and 7 years of follow-up, respectively (Table 3).

Adverse Events
In 37 patients (62%), 53 adverse events occurred, and 38 events (72%) were classified as severe (Table 4). Ten adverse events occurred during the perioperative phase and 43 events during the follow-up period.

Survival free of any adverse event after discharge was 90%, 78%, 56%, and 42% (Figure 3), whereas survival free

### Table 2. Intraoperative Results of ICD Implantation

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>RV Lead Positions, n</th>
<th>R-Wave Amplitude, mV</th>
<th>Pacing Threshold, mA at 0.5 ms</th>
<th>DFT, J</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVC 60</td>
<td>3.1±3.1*</td>
<td>10.5±2.9†</td>
<td>0.66±0.28</td>
<td>11.1±5.8</td>
</tr>
<tr>
<td>CAD 672</td>
<td>2.3±2.2</td>
<td>13.7±5.3</td>
<td>0.74±0.44</td>
<td>12.5±5.8</td>
</tr>
<tr>
<td>DCM 232</td>
<td>2.3±2.1</td>
<td>13.1±5.1</td>
<td>0.74±0.43</td>
<td>13.0±5.8</td>
</tr>
<tr>
<td>Other 249</td>
<td>2.4±2.4</td>
<td>12.6±4.7</td>
<td>0.71±0.40</td>
<td>12.0±5.6</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.001 vs other groups (ANOVA).

### Table 3. Long-term Follow-up Results After ICD Implantation in 60 Patients With ARVC

<table>
<thead>
<tr>
<th>Years After ICD Implantation</th>
<th>1 (n=55)</th>
<th>3 (n=49)</th>
<th>5 (n=40)</th>
<th>7 (n=29)</th>
<th>10 (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>100</td>
<td>94</td>
<td>94</td>
<td>87</td>
<td>76</td>
</tr>
<tr>
<td>Estimated ICD benefit</td>
<td>21</td>
<td>32</td>
<td>36</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>Fast VT/VF</td>
<td>79</td>
<td>64</td>
<td>59</td>
<td>56</td>
<td>52</td>
</tr>
<tr>
<td>Any VT/VF</td>
<td>49</td>
<td>30</td>
<td>26</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>VT cluster</td>
<td>83</td>
<td>73</td>
<td>69</td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td>Any AE</td>
<td>90</td>
<td>78</td>
<td>56</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>Severe AE</td>
<td>90</td>
<td>82</td>
<td>64</td>
<td>56</td>
<td>50</td>
</tr>
<tr>
<td>Lead-related AE</td>
<td>95</td>
<td>85</td>
<td>74</td>
<td>63</td>
<td>53</td>
</tr>
<tr>
<td>Undersensing</td>
<td>96</td>
<td>95</td>
<td>92</td>
<td>89</td>
<td>86</td>
</tr>
</tbody>
</table>

AE indicates adverse event. Results are given as percentage for estimated benefit of ICD therapy on survival from life-threatening VT/VF (see text for details) or freedom from events; n indicates number of patients.

![Figure 1](image-url). Mortality and recurrence of VT or VF during follow-up (80±43 months) after ICD implantation in ARVC. Kaplan-Meier curves depict event-free survival for all-cause mortality, fast VT/VF (>240 bpm), and VT/VF at any rate.
of severe complications was 90%, 82%, 64%, and 56% after 1, 3, 5, and 7 years, respectively (Table 3). In 18 patients (30%), 25 episodes of VT clusters (frequent ICD therapies within 24 hours) occurred during the perioperative period (n=5) and the follow-up period (n=20). These VT clusters were controlled by antiarrhythmic drugs (n=20) or radiofrequency catheter ablation of the predominant arrhythmia focus (n=5).

After discharge, 31 lead-related adverse events occurred in 21 patients (35%) after 49±35 months (range, 5 to 125 months; median, 52 months) of follow-up. These adverse events were not related to specific lead designs or models. Freedom from lead-related complications was 95%, 85%, 74%, and 63% after 1, 3, 5, and 7 years (Figure 3, Table 3).

### Inappropriate ICD Therapies

Fourteen patients (23%) received inappropriate ICD shocks during follow-up. These were due to exercise-related sinus tachycardia (n=4), atrial fibrillation with fast AV conduction (n=3), or oversensing (n=7).

### Discussion

In patients with ARVC, ICD therapy is increasingly used, but information on long-term results and complications is limited. No prospective randomized trials have compared ICD therapy with treatment with antiarrhythmic drugs or catheter ablation in ARVC. The present study represents the largest single-center experience with ICD therapy in ARVC available to date. It comprises a considerable number of 60 well-characterized consecutive high-risk patients with the rare condition of ARVC and provides almost complete long-term follow-up information on recurrent ventricular tachyarrhythmias and complications after ICD implantation, mainly indicated for secondary prevention after resuscitated cardiac arrest or sustained VT. The results highlight the beneficial role of ICD therapy in ARVC with respect to arrhythmic events and survival but also indicate a considerable cumulative incidence of lead-related complications during extended long-term follow-up in this young patient population.

### Results of ICD Therapy

The results of the present study confirm and largely extend our previous preliminary reports and 2 smaller series on ICD therapy in ARVC. Link et al described 12 patients with ARVC after ICD implantation (4 with epicardial leads) and a
follow-up of 22±13 months. One patient died suddenly 1 month after implantation (electrical storm), and 7 patients had appropriate device therapies. Complications included inappropriate ICD shock delivery because of supraventricular arrhythmias or insulation failure of transvenous (n=4) or epicardial (n=1) leads. Tavernier et al8 described 9 patients with ARVC after ICD implantation. After follow-up of 32±24 months, all patients were alive. Complications of ICD therapy were not reported. Appropriate ICD therapies included antitachycardia pacing in 6 patients and cardioversion in 4 patients. Six patients experienced 22 inappropriate ICD interventions.

In our series, the majority of patients with ARVC received appropriate ICD therapies early during follow-up, as indicated by the low event-free survival rates and the relevant estimated survival benefit early and late after ICD implantation. There were no procedure-related deaths.

Concern has been raised about the potential risk of RV perforation, adequate placement, and long-term performance of transvenous leads in the diseased and potentially thinned RV myocardium in ARVC.7,9,16 Perforation of transvenous ICD leads has been reported, with an incidence of 0.6% to 5.2% in large populations,17,18 but was not observed in our patients with ARVC.

However, the diseased RV myocardium in ARVC may render adequate RV lead placement more difficult to achieve satisfactory sensing, pacing, and defibrillation results. Therefore, we recommend detailed intraoperative testing and the use of screw-in leads. Although we tested a higher number of RV sites in the present study, a lower final R-wave amplitude during follow-up, which may not compromise adequate device function but may also indicate disease progression.

An increase in failure rates of transvenous leads has been reported beyond 4 to 5 years after implantation.19–22 Ellenhogen et al21 recently reported a cumulative lead failure probability of 37% after 69 months and discussed lead failure as a significant problem late after ICD implantation. Dorwarth et al22 published similar results with an increase of lead failure from 2% at 4 years to 38% at 8 years of follow-up. The present study in ARVC is in agreement with these reports and also indicates a high rate of lead-related complications (37% at 7 years) during extended long-term follow-up of up to 12 years. The disease-specific problem of progressive undersensing contributes further to the high failure rates of ICD leads in ARVC.

Study Limitations
The present study is a single-center experience, related mainly to secondary prevention. The patient characteristics and indications for ICD implantation may express referral bias and institutional preferences. In addition, different devices, leads, and surgical techniques were used during the long implantation period of up to 12 years, with potential impact on the incidence of adverse events. With improvements of lead designs, lead fracture or insulation defects may occur less frequently in the future, whereas infection, thrombosis, and undersensing may remain relevant problems during long-term follow-up after ICD implantation in ARVC.

The concept of hypothetical death is controversial because it assumes that VT recurrences >240 bpm would have been fatal in all cases without treatment by the ICD.14 However, despite preserved left ventricular function in ARVC, this concept remains rather conservative because it also assumes that no VT with a rate of ≤240 bpm would have resulted in sudden death. In our study, 17 of 24 patients with ARVC and fast VT had ventricular flutter or fibrillation during the episode. Therefore, calculation of benefit on survival of life-threatening VT/VF may allow an assessment of improved prognosis by the ICD in patients with ARVC as well.

Considerations for ICD Therapy in ARVC
There is no doubt that the ICD can effectively terminate malignant ventricular tachyarrhythmias. However, the most relevant clinical question is whether in a given population the ICD reduces all-cause mortality with an acceptable risk of complications and side effects compared with the best medical therapy. On the one hand, pharmacological therapy yields limited efficacy and potential side effects. In particular, long-term treatment with amiodarone is associated with a high incidence of adverse effects and subsequent treatment discontinuation,23 which may be even more relevant in young populations with a need for long-term treatment. On the other hand, when ICD implantation is considered, a correct diagnosis of ARVC on the basis of detailed investigations is essential because the main differential diagnosis of idiopathic right ventricular tachycardia has a more favorable prognosis and the option of curative treatment by catheter ablation.

Accepted indications for ICD implantation in ARVC include secondary prevention after survived cardiac arrest and/or sustained VT. In these patients, life-threatening recurrences of sustained VT/VF are frequent, and ICD therapy is safe and efficacious in the termination of these arrhythmias by cardioversion or antiarrhythmic pacing. In contrast, the role of ICD implantation for primary prevention in asymptomatic ARVC patients or relatives with a high-risk profile remains controversial. Because no data are available to generally support this approach, the decision to implant an ICD must be based on individual risk assessment, physician judgment, and patient preference.

Dual-chamber ICD systems may reduce inappropriate ICD therapies through improved differentiation of ventricular and supraventricular arrhythmias and have therefore also been
recommended in ARVC. However, because of the relevant incidence of lead-related complications during long-term follow-up in young patients with ARVC, dual-chamber ICDs were infrequently used in the present study. Our strategy followed a more conservative approach, aiming at a reduction in the number of implanted leads.

To further optimize the therapeutic management of patients with ARVC, more detailed data on the natural history and long-term prognosis and improvement of risk stratification are required. Data from larger numbers of patients and affected families, possibly from multicenter studies or registries, will be essential to establish more clear-cut recommendations for selection of the most appropriate patients for ICD therapy versus medical or other nonpharmacological treatment options in ARVC.

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