Efficacy of Antiarrhythmic Drugs in Patients With Arrhythmogenic Right Ventricular Disease

Results in Patients With Inducible and Noninducible Ventricular Tachycardia

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Background. Ventricular tachyarrhythmias are the major clinical manifestation of arrhythmogenic right ventricular disease. Although antiarrhythmic therapy has been widely advocated, there is only limited information available on the efficacy of antiarrhythmic drugs in these patients.

Methods and Results. The short- and long-term efficacies of various antiarrhythmic agents were retrospectively and prospectively analyzed in 81 patients (mean age, 39±14 years; range, 16–68 years; 61.7% males) with arrhythmogenic right ventricular disease. In 42 patients with inducible ventricular tachycardia during programmed ventricular stimulation, the following efficacy rates were obtained: class Ia and Ib drugs (n=18), 5.6%; class Ic drugs (n=25), 12%; β-blockers (n=8), 0%; sotalol (n=38), 68.4%; amiodarone (n=13), 15.4%; verapamil (n=5), 0%; and drug combinations (n=26), 15.4%. Only one of the 10 patients not responding to sotalol was treated effectively by amiodarone, whereas the remaining nine patients proved to be drug refractory toward all other drugs tested (3.8±2.3 drugs, including amiodarone in five cases) and underwent nonpharmacological therapy. During a follow-up of 34±25 months, three of the 31 patients (9.7%) discharged on pharmacological therapy had nonfatal recurrences of ventricular tachycardia after 0.5, 51, and 63 months, respectively. In 39 patients with noninducible ventricular tachycardia during programmed ventricular stimulation, the following efficacy rates were observed: class Ia and Ib drugs (n=16), 0%; class Ic agents (n=23), 17.4%; β-blockers (n=7), 28.6%; sotalol (n=35), 82.8%; amiodarone (n=4), 25%; verapamil (n=24), 50%; and drug combinations (n=11), 9.1%. During a follow-up of 14±13 months, four of 33 patients (12.1%) discharged on antiarrhythmic drugs had nonfatal relapses of their clinical ventricular arrhythmia.

Conclusions. Thus, in arrhythmogenic right ventricular disease, sotalol proved to be highly effective in patients with inducible as well as noninducible ventricular tachycardia. Patients with inducible ventricular tachycardia not responding to sotalol are likely to not respond to other antiarrhythmic drugs and should be considered for nonpharmacological therapy without further drug testing. Amiodarone did not prove to be more effective than sotalol and may not be an alternative because of frequent side effects during long-term therapy, especially in young patients. Verapamil and β-blockers were effective in a considerable number of patients with noninducible ventricular tachycardia and may be a therapeutic alternative in this subgroup. Class I agents appear to be rarely effective in the treatment of both inducible and noninducible ventricular tachycardia in arrhythmogenic right ventricular disease. (Circulation 1992;86:29–37)

Key Words • right ventricle • dysplasia, right ventricular • antiarrhythmics • ventricular tachycardia

Arrhythmogenic right ventricular disease (ARVD) is a rare myocardial disorder characterized by ventricular tachyarrhythmias originating from the right ventricle, frequent repolarization abnormalities in the right precordial leads of the surface ECG, and localized or diffuse right ventricular contraction abnormalities detectable by two-dimensional echocardiography, gated nuclear scintigraphy, or right ventricular angiography. The underlying structural cardiac abnormalities may be examined by endomyocardial biopsy or, more recently, magnetic resonance imaging.

Patients with arrhythmogenic right ventricular disease and inducible ventricular tachycardia normally present with spontaneous sustained monomorphic ventricular tachycardia. They frequently exhibit more extensive global or regional right ventricular contraction abnormalities detectable by various imaging techniques. In contrast, patients with noninducible ventricular tachycardia normally present with frequent ventricular runs or repetitive nonsustained ventricular tachycardia and only circumscribed contraction abnormalities of the right ventricle, mostly not reducing global right ventricular ejection fraction.
Antiarrhythmic drug therapy frequently is considered to be indicated in patients with arrhythmogenic right ventricular disease to prevent serious arrhythmic symptoms or complications including sudden cardiac death, which has been reported in both subgroups.\textsuperscript{16,17} Although various authors have reported on successful antiarrhythmic therapy with various drugs and drug combinations in small numbers of patients, pharmacological treatment still is empiric.\textsuperscript{14,15,18–23} Recommendations concerning the most effective drugs and dosages have not been established. Therefore, we analyzed retrospectively and prospectively the short- and long-term efficacies of different antiarrhythmic drugs in 81 patients with arrhythmogenic right ventricular disease and inducible or noninducible ventricular tachycardia during programmed ventricular stimulation.

**Methods**

**Study Patients**

The study population comprised 81 patients (50 males and 31 females) ranging in age from 16 to 68 years (mean, 39±13.9 years) with proven or highly suspected arrhythmogenic right ventricular disease on the basis of the 12-lead surface ECG during sinus rhythm and documented sustained or nonsustained ventricular tachycardia (n=81), noninvasive imaging techniques such as two-dimensional echocardiography (n=81) and magnetic resonance imaging (n=50), right and left ventricular angiography and coronary angiography (n=81), and endomyocardial biopsy (n=64). The first patient included in this study was diagnosed in 1977. The baseline characteristics of the patients are summarized in Table 1.

**Diagnosis of Arrhythmogenic Right Ventricular Disease**

Arrhythmogenic right ventricular disease was diagnosed in the presence of documented sustained or nonsustained ventricular tachycardia of left bundle branch block morphology, repolarization abnormalities in the right precordial leads of the surface ECG in sinus rhythm, and evidence of characteristic right ventricular contraction abnormalities. Coronary artery disease, dilative or hypertrophic cardiomyopathy, and congenital or acquired valvular heart disease were excluded. The more specific diagnosis of arrhythmogenic right ventricular dysplasia was made in the presence of the above-mentioned criteria and the additional evidence of abnormal fibrolipomatous infiltration of the right ventricular myocardium,\textsuperscript{3,4} which was detected by endomyocardial biopsy in 35 of 64 patients (54.7%). Patients with idiopathic ventricular tachycardia that was diagnosed after exclusion of morphological, functional, and structural heart disease\textsuperscript{3} were not included in this study.

Characteristic angiographic findings suggestive of arrhythmogenic right ventricular disease were localized akinesia, dyskinesia, aneurysms, bulgings, or outpouchings,\textsuperscript{24–27} which may also be detectable by two-dimensional echocardiography.\textsuperscript{28–32} In addition, nonspecific angiographic findings like horizontal fissures and slow dye evacuation frequently were observed. Angiographic global ejection fractions were determined uniplane for the left ventricle by calculation according to the area-length method and biplane for the right ventricle according to Boak's formula.\textsuperscript{33} Endomyocardial biopsies were taken from different right ventricular areas (3.4±1.6 samples per patient; range, one to eight) by preference of regions of documented contraction abnormalities.

**Electrophysiological Study**

All patients underwent an invasive electrophysiological study with programmed ventricular stimulation off antiarrhythmic drugs in the nonsedated state after written informed consent was obtained. Single and double extrastimuli were delivered at two right ventricular stimulation sites (apex and outflow tract) at twice-diastolic threshold during sinus rhythm and basic drive cycle lengths of 500, 430, 370, and 330 msec.\textsuperscript{34} If no sustained ventricular tachycardia was inducible, a third extrastimulus was introduced during 500-msec drive cycle length. If still no ventricular tachycardia was inducible, the entire sequence was repeated after intravenous isoprenaline infusion titrated to achieve an increase of basic heart rate by 25% or more.

**Definitions**

Spontaneous and induced ventricular tachyarrhythmias were classified according to the definitions listed in Table 2.

**Criteria of Drug Efficacy**

Various antiarrhythmic drugs of different classes of action according to the classification of Vaughan-Williams\textsuperscript{35} were used in both patient groups. The drugs and

\begin{table}
\centering
\begin{tabular}{lccc}
& VT inducible & VT noninducible & \\
& (n=42) & (n=39) & \\
\hline
Male (%) & 85.7 & 35.9 & <0.001 \\
Age at onset of symptoms (mean±SD, years) & 34±14.1 & 34±13.5 & NS \\
Age at diagnosis (mean±SD, years) & 38±14.5 & 40±13.3 & NS \\
Presenting arrhythmia: sustained VT (%) & 92.9 & 20.5 & <0.0001 \\
Presenting arrhythmia: nonsustained VT (%) & 7.1 & 79.5 & <0.0001 \\
Antiarrhythmic drugs tested (mean±SD) & 4.3±3.5 & 3.9±2.8 & NS \\
Abnormal fibrolipomatosis (%) & 43.3 (n=30) & 64.7 (n=34) & NS \\
RV-EF (mean±SD, %) & 45±8.3 & 56±6.1 & <0.0001 \\
LV-EF (mean±SD, %) & 70±11.2 & 74±8.7 & NS \\
\end{tabular}
\caption{Clinical Characteristics of Study Patients}
\end{table}
TABLE 2. Definitions

<table>
<thead>
<tr>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular run</td>
<td>3–10 consecutive ventricular beats</td>
</tr>
<tr>
<td>Nonsustained VT</td>
<td>≥10 consecutive ventricular beats, &lt;30 seconds' duration</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>&gt;30 seconds' duration or prior termination because of hemodynamic deterioration</td>
</tr>
<tr>
<td>Inducible VT</td>
<td>Sustained VT inducible by PVS at baseline or after isoprenaline infusion</td>
</tr>
<tr>
<td>Noninducible VT</td>
<td>No sustained VT inducible by PVS including isoprenaline infusion</td>
</tr>
</tbody>
</table>

VT, ventricular tachycardia; PVS, programmed ventricular stimulation.

corresponding mean daily dosages are listed in Tables 3 and 4.

In the retrospective part of data analysis, information on all previously administered drugs were extracted from the records of the referring physicians and hospitals and by interviewing the patients. Clinical drug failure was defined as recurrence of ventricular tachycardia despite regular drug intake and adequate dosages. Blood levels were not available.

In the prospective part of data analysis, patients with inducible ventricular tachycardia underwent antiarrhythmic drug testing guided by serial programmed ventricular stimulation. Drug efficacy was judged according to criteria previously reported and shown in Figure 1. In patients with noninducible ventricular tachycardia, drug therapy was guided by repeated 48-hour Holter monitoring and symptom-limited treadmill exercise tests. The efficacy criteria used for analysis are shown in Figure 2.

Follow-up

End points for follow-up were either spontaneous recurrences of ventricular tachycardia or sudden death and cardiac or noncardiac death or the time of study closure. No patient was lost to follow-up. In patients who discontinued electrophysiologically or clinically tested and effective antiarrhythmic drug therapy, follow-up ended at the time of drug withdrawal. The follow-up data were obtained by regular follow-up visits at our institution and telephone contact with the patients and their physicians at regular intervals.

Results

Results of Control Electrophysiological Study

During the control electrophysiological study, 42 of 81 patients (36 men; mean age at diagnosis, 38±14.5 years) had inducible sustained ventricular tachyarrhythmias (monomorphic ventricular tachycardia, n=39 [92.8%]; mean cycle length, 291±71 msec [190–530 msec]; polymorphic ventricular tachycardia, n=1 [2.4%]; ventricular fibrillation, n=2 [4.8%]). These ventricular tachyarrhythmias were induced from the right ventricular apex in 37 patients (88.1%) and from the right ventricular outflow tract in the remaining five patients (11.9%). Their induction required single extrastimuli in six patients (14.3%), double in 31 (73.8%), triple in five (11.9%), and isoprenaline infusion in four

TABLE 3. Drugs and Dosages Used in Patients With Inducible Ventricular Tachycardia

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>No. of patients</th>
<th>Dosage (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Disopyramide</td>
<td>10</td>
<td>594±138</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>1</td>
<td>600</td>
</tr>
<tr>
<td>Ib</td>
<td>Tocainide</td>
<td>1</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>Mexiletine</td>
<td>16</td>
<td>700±135</td>
</tr>
<tr>
<td>Ic</td>
<td>Propafenone</td>
<td>20</td>
<td>728±196</td>
</tr>
<tr>
<td></td>
<td>Flecainide</td>
<td>17</td>
<td>250±50</td>
</tr>
<tr>
<td></td>
<td>Aprindine</td>
<td>8</td>
<td>113±23</td>
</tr>
<tr>
<td></td>
<td>Prajmaline</td>
<td>7</td>
<td>107±41</td>
</tr>
<tr>
<td></td>
<td>Lorcanide</td>
<td>3</td>
<td>333±153</td>
</tr>
<tr>
<td></td>
<td>Diprafenone</td>
<td>1</td>
<td>600</td>
</tr>
<tr>
<td></td>
<td>Barucaiden</td>
<td>1</td>
<td>450</td>
</tr>
<tr>
<td>III</td>
<td>Sotalol</td>
<td>38</td>
<td>459±100</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>13</td>
<td>400±155*</td>
</tr>
<tr>
<td>IV</td>
<td>Verapamil</td>
<td>5</td>
<td>300±120</td>
</tr>
</tbody>
</table>

*After a loading phase of 1,000 mg/day for 21 days. Values are given as mean±SD.

VT inducibility during PVS compared to baseline

none more difficult unchanged

spontaneous recurrence

FIGURE 1. Chart of criteria of drug efficacy in patients with inducible ventricular tachycardia (VT). A response to a drug was considered to be present if VT was no longer inducible or rendered more difficult to induce. Drug failure was present if there was unchanged inducibility or a spontaneous recurrence of VT. PVS, programmed ventricular stimulation.
Sotalol treatment resulted in the highest overall efficacy rate (68.4%). Complete suppression was achieved in 22 of 38 patients (57.9%), and partial response was achieved in another four patients (10.5%). In only three of 12 patients not responding to monotherapy with oral sotalol, ventricular tachycardia induction was suppressed completely by amiodarone (n=1) or a combination of sotalol with class I agents (n=2), whereas the remaining nine patients proved drug refractory after serial testing with 3.8±2.3 drugs, including amiodarone in five cases. Nonpharmacological therapy was performed in eight of these patients. The remaining patient was discharged on sotalol despite persistent ventricular tachycardia induction.

Amiodarone proved to be effective according to the electrophysiological criteria in only two of 13 patients (15.4%). Ventricular tachycardia induction was unchanged in nine patients, six of whom had spontaneous ventricular tachycardia recurrences after 7±7 months (range, 1–18 months) during a total follow-up of 17±19 months (range, 1–51 months). The remaining two patients were followed clinically without programmed ventricular stimulation after the loading phase. Both had spontaneous ventricular tachycardia relapses after 3 and 12 months, respectively, and amiodarone treatment was discontinued.

Class Ia and Ib drugs as well as class Ic agents were effective in only 5.6% and 12.0%, respectively. Because several patients received more than one drug of the same group, the total number of drug tests exceeded the number of patients. Only one of 28 tests (3.6%; disopyramide) performed with class Ia or Ib drugs and three of 57 tests (5.3%; flecainide, propafenone, aprindine) with class Ic agents were successful.

β-Blockers (n=7) and verapamil (n=5) failed in all patients treated.

Drug combinations were effective in four of 26 patients (15.4%) in whom the individual agents had previously failed. Combinations of class I drugs with sotalol (n=10) or amiodarone (n=4) were effective in two patients each, whereas combinations of two class I drugs (n=5) or class I drugs with β-blockers (n=7) showed no beneficial effect.

Follow-up. Thirty-one of 42 patients (73.8%) with inducible ventricular tachycardia were discharged on pharmacological treatment guided by serial drug testing, whereas the remaining 11 patients (26.2%) were

Table 5. Efficacy of Antiarrhythmic Drugs in Patients With Inducible Ventricular Tachycardia

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of patients</th>
<th>Overall efficacy</th>
<th>Complete suppression</th>
<th>Partial response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class Ia/b</td>
<td>18</td>
<td>1</td>
<td>5.6</td>
<td>0</td>
</tr>
<tr>
<td>Class Ic</td>
<td>25</td>
<td>3</td>
<td>12.0</td>
<td>1</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sotalol</td>
<td>38</td>
<td>26</td>
<td>68.4</td>
<td>22</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>13</td>
<td>2</td>
<td>15.4</td>
<td>2</td>
</tr>
<tr>
<td>Verapamil</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Combinations</td>
<td>26</td>
<td>4</td>
<td>15.4</td>
<td>2</td>
</tr>
<tr>
<td>Two class I drugs</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Class I+β-blocker</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Class I+sotalol</td>
<td>10</td>
<td>2</td>
<td>20.0</td>
<td>2</td>
</tr>
<tr>
<td>Class I+amiodarone</td>
<td>4</td>
<td>2</td>
<td>50.0</td>
<td>0</td>
</tr>
</tbody>
</table>
considered drug refractory and were treated with alternative modalities such as catheter ablation \((n=9)\), anti-tachycardia surgery \((n=1)\), or implantation of a cardioverter-defibrillator \((n=1)\). At the time of discharge, 21 patients received oral sotalol alone, and four patients received sotalol in combination with a class I drug (aprindine, \(n=3\); mexiletine, \(n=1\)). The remaining six patients were treated with amiodarone \((n=2)\), class Ic drugs \((n=2)\); propafenone, flecaïnine), or a combination of amiodarone and class Ic drugs \((n=2)\); propafenone, flecaïnine). During a mean follow-up of 34±25 months (range, 2–103 months), there were no sudden cardiac deaths or cardiac or noncardiac deaths in these 31 patients discharged on pharmacological therapy. Three patients \((9.7\%)\) had nonfatal recurrences of ventricular tachycardia after 0.5, 51, and 63 months, one of which was associated with hypokalemia.

### Efficacy of Antiarrhythmic Drugs in Noninducible Ventricular Tachycardia

**Acute response.** In 39 patients with noninducible ventricular tachycardia, a total of 148 drug tests were performed (Table 6). Prospective analysis of drug efficacy included 91 drug tests in these 39 patients, whereas the remaining 57 drug tests were evaluated retrospectively in 17 patients.

The overall efficacy rate for sotalol was 82.8% with a complete suppression of frequent ventricular runs and nonsustained or sustained ventricular tachycardia in 23 of 35 patients \((65.7\%)\) and a partial response in an additional six patients \((17.1\%)\). Only one of four patients was effectively treated with amiodarone. β-Blockers showed a partial effect in two of seven patients \((28.6\%)\), and verapamil was effective in 12 of 24 patients \((50.0\%)\), half of them meeting the criteria of complete arrhythmia suppression. Class Ia and Ib antiarrhythmic drugs were not effective in any of 16 patients \((5.5\%)\) of total number of drug tests, 26), whereas class Ic agents were effective in four of 23 patients \((17.4\%)\) in a total number of 41 drug tests \((9.8\%\) effective tests; propafenone, \(n=2\); flecaïnine, \(n=2\)). Drug combinations showed partial response in one of 11 patients \((9.1\%\); amiodarone with flecaïnine) despite previous failure of the individual drugs.

**Follow-up.** At the time of discharge, 33 of 39 patients \((84.6\%)\) with noninducible ventricular tachycardia were treated pharmacologically. Twenty-four patients received oral sotalol, seven patients received verapamil, and two patients received class Ic agents (propafenone, flecaïnine). Two patients with clinically asymptomatic short ventricular runs were discharged without treatment. Both are doing well after 6 and 21 months of follow-up. The remaining four patients with symptomatic ventricular tachycardia did not respond to pharmacological treatment and underwent catheter ablation.

During a mean follow-up of 14±13 months (range, 2–65 months), there were no sudden cardiac deaths and no cardiac or noncardiac deaths in these 33 patients discharged on antiarrhythmic drug therapy. Four patients \((12.1\%)\) had nonfatal recurrences of ventricular tachycardia. Recurrences occurred in two of 24 patients \((8.3\%)\) discharged on sotalol and in two of seven patients \((28.6\%)\) discharged on verapamil. At the time of discharge, drug therapy had been judged as completely effective in three of them and partially effective in the remaining patient.

### Side Effects

During treatment with class I drugs, gastrointestinal side effects demanded discontinuation of therapy in five of 54 patients \((9.3\%)\) or five of 152 drug tests \((3.3\%)\). Sotalol had to be withdrawn in four of 73 patients \((5.5\%)\) because of symptomatic bradycardia \((n=1)\), hypotension \((n=1)\), pulmonary congestion \((n=1)\), and QT prolongation with torsade de pointes \((n=1)\). Atrio-ventricular conduction disturbances were not observed. In all except one patient, side effects occurred during the first days of therapy during hospital stay. Thus, during a total follow-up of 25±22 months, only one of 49 patients discharged on sotalol developed serious side effects (symptomatic hypotension) after discharge. Amiodarone treatment was discontinued in five of 17 patients \((29.4\%)\) because of serious side effects (hyperthyroidism, \(n=3\); hepatotoxicity, \(n=1\); ophthalmic toxicity with symptomatic corneal deposits, \(n=1\)) during long-term therapy after 24±24 months (range, 2–51 months). No serious adverse effects were observed during treatment with β-blockers or verapamil.

### Discussion

Ventricular tachyarrhythmias are the major clinical manifestation of arrhythmogenic right ventricular disease. The documented arrhythmia may range from frequent premature ventricular complexes, ventricular
runs, and nonsustained ventricular tachycardia to sustained ventricular tachycardia.\cite{12,26,37} Primary ventricular fibrillation has been reported in single cases but appears to be rare.\cite{38-41} The right ventricular origin of the arrhythmias is suggested by the left bundle branch block morphology of ventricular tachycardia and can be confirmed by detailed endocardial catheter mapping techniques.

Although some patients do not report any symptoms suggestive of arrhythmias, the majority of patients present clinically with either palpitations, dizziness, syncope, or even sudden death. Patients with inducible ventricular tachycardia during programmed ventricular stimulation normally present with spontaneous sustained monomorphic ventricular tachycardia. They frequently exhibit pronounced global or regional right ventricular contraction abnormalities detectable by various imaging techniques. In contrast, patients with noninducible ventricular tachycardia normally present with repetitive ventricular runs or nonsustained ventricular tachycardia and only mild or moderate right ventricular contraction abnormalities, which may only be detectable by biplane right ventricular angiography.\cite{12-15} However, due to the variable appearance of a normal right ventricle, differentiation of abnormal from normal right ventricular contractions may be difficult in patients with very mild angiographic findings. Because circumscribed right ventricular contraction abnormalities do not necessarily result in a reduction of global right ventricular function, the right ventricular ejection fraction is within normal limits in most patients with noninducible ventricular tachycardia.

The need for antiarrhythmic therapy has been advocated in both subgroups of arrhythmogenic right ventricular disease because of symptoms and possibly prognostic aspects since sudden cardiac death may occur in both patient groups.\cite{16,17} However, specific risk factors for the selection of patients at high risk of sudden cardiac death have not been defined. The experiences with the use of antiarrhythmic drugs in patients with coronary artery disease or cardiomyopathies are not necessarily transferable to patients with arrhythmogenic right ventricular disease. Because information on the use of antiarrhythmic drugs in these patients is limited, this study was performed to analyze and discuss the short- and long-term effects of antiarrhythmic drug therapy in 81 patients with arrhythmogenic right ventricular disease.

Overall, 64 of 81 patients (79.0%) who were referred for further treatment, responded acutely to antiarrhythmic drug therapy without limiting side effects, whereas 15 patients (18.5%) were subjected to nonpharmacological therapy, and two patients (2.5%) were discharged without treatment.

Class I antiarrhythmic drugs have been demonstrated to be effective during electrophysiological testing in the treatment of life-threatening ventricular tachyarrhythmias in various underlying heart diseases. Most available data refer to postmyocardial infarction ventricular tachyarrhythmias and less frequently to patients with dilative cardiomyopathy.\cite{42-45} However, in patients with arrhythmogenic right ventricular disease, varying results have been reported.\cite{13,14,19,21} In our patients with inducible as well as noninducible ventricular tachycardia, class I antiarrhythmic drugs proved effective in only a minority of patients. Effective treatment with class I agents was achieved in only four of 85 drug tests (4.7%) performed in 27 patients with inducible ventricular tachycardia and in only five of 67 drug tests (7.5%) in 27 patients with noninducible ventricular tachycardia. The overall efficacy rates were 14.8% and 18.5% of patients, respectively, markedly lower than those reported in the treatment of ischemic ventricular tachycardia, although various class I agents were tested, and some patients received three or more different class I drugs successively without satisfactory therapeutic effect. Class Ic agents appeared to be slightly more effective than class Ia and Ib drugs; this has also been reported by others.\cite{45,46}

\textit{$\beta$-Blockers}, which were tested in only a small group of patients, did not have sufficient antiarrhythmic effect in those with inducible ventricular tachycardia but were at least partially effective in a small number of patients with noninducible ventricular tachycardia (28.6%). This corresponds to studies in patients with idiopathic ventricular tachycardia, possibly by an inhibition of catecholamine-induced increase of intracellular cyclic AMP mediated by GTP-dependent regulatory proteins.\cite{37-40}

Our results demonstrate that oral sotalol administered in dosages ranging from 320 to 480 mg/day (up to 640 mg/day in selected cases) appears to be the most effective antiarrhythmic drug in the treatment of both inducible and noninducible ventricular tachycardia in arrhythmogenic right ventricular disease. The overall efficacy rates were 68.4% and 82.8%, respectively. Side effects demanding withdrawal of sotalol treatment were rare (5.5%) and mostly occurred within the first days of therapy. High efficacy rates of sotalol compared with other antiarrhythmic agents may not be unique in the condition of arrhythmogenic right ventricular disease because similar overall efficacy rates of 61% were observed in our group of 171 patients with inducible ventricular tachycardia and various underlying heart diseases (68% coronary artery disease).\cite{50} Serious side effects were observed in only nine of these 171 patients (5.3%) despite considerably high dosages of sotalol, which also confirms the low rate of adverse effects reported in the present study. Sotalol dosages of more than 320–480 mg/day clearly exceed the dosage necessary for $\beta$-blockade,\cite{51} so that its antiarrhythmic efficacy may predominantly be attributed to its class III activity. All except one patient with inducible ventricular tachycardia not responding to oral sotalol or combinations with sotalol proved refractory against all other antiarrhythmic agents tested (including amiodarone). Therefore, nonpharmacological therapy without further serial drug testing should be considered in sotalol nonresponders with inducible ventricular tachycardia.

Amiodarone did not seem to be superior to sotalol. Of 12 patients receiving both drugs successively, one of eight sotalol nonresponders was effectively treated with amiodarone, whereas two of nine amiodarone nonresponders were effectively treated with sotalol. With regard to its potential side effects during long-term therapy,\cite{52} amiodarone does not appear to be the drug of first choice in the treatment of young patients requiring long-term antiarrhythmic drug therapy.

Verapamil has been reported to be effective in a considerable percentage of patients with various forms of nonischemic ventricular tachycardia, especially right
ventricular outflow tract tachycardia.\textsuperscript{19,20,53–57} In our study group, 50\% of patients with noninducible ventricular tachycardia responded to verapamil, and 92\% of them met the criteria of repetitive nonsustained ventricular tachycardia originating in the right ventricular outflow tract. The mechanism of these tachycardias is postulated to be due to catecholamine-induced delayed afterdepolarizations dependent on intracellular calcium overload. Adenosine appears to be highly effective in specifically inhibiting cyclic AMP through an inhibitory G protein and therefore is effective only in the termination of ventricular tachycardia due to cyclic AMP–mediated triggered activity. By blocking the slow-inward calcium current and therefore preventing intracellular calcium overload, verapamil is effective in calcium-induced, ouabain-induced, and catecholamine–cyclic AMP–mediated triggered activity.\textsuperscript{47,58} Only a few of our patients with inducible ventricular tachycardia received verapamil, which does not permit any definite conclusions. However, none of the patients in this group responded to verapamil.

A combination of antiarrhythmic drugs may result in electrophysiological and antiarrhythmic properties that may be different from the actions of the individual agents. Drug combination may cause enhanced or decreased antiarrhythmic efficacy but also may increase or decrease the incidence of side effects, depending on the dosage of the individual drugs.\textsuperscript{59–64} In this regard, our experience with antiarrhythmic drug combinations in patients with arrhythmogenic right ventricular disease is limited. These limited observations in patients on combination therapy did not appear to be promising. Drug combinations with class I drugs and amiodarone or sotalol were effective in a minority of patients in whom the individual drugs had previously failed, whereas combinations of two class I drugs and class I drugs with \(\beta\)-blockers were not effective in any of the patients treated. This contrasts with the results of French authors who reported satisfactory therapeutic effects of combined therapy with class I agents and \(\beta\)-blockers.\textsuperscript{23}

Our experience in the use of drug combinations with amiodarone is supported by the same authors who also found an increase of amiodarone efficacy by additional therapy with class I drugs in single patients. The combination of amiodarone with \(\beta\)-blockers may be more effective than the individual drugs.\textsuperscript{22,23} In a study by Leclercq et al.,\textsuperscript{23} all of the six patients previously insufficiently treated by class I agents, amiodarone, or \(\beta\)-blockers alone or by combinations of class I agents with \(\beta\)-blockers or amiodarone proved to be effectively treated with the combination of amiodarone and \(\beta\)-blockers. These observations should be viewed in the light of our positive results with high dosages of sotalol. Both therapeutic regimen consist in a combination of class III and \(\beta\)-blocking antiarrhythmic properties, which appears to act synergistically in patients with arrhythmogenic right ventricular disease. This may be due to the strong catecholamine dependence as a triggering factor for ventricular arrhythmia in many of these patients, uncovered by stress tests or isoproterenol infusion.\textsuperscript{65–68}

The low incidence of recurrences of ventricular tachyarrhythmias and the absence of sudden deaths during follow-up of our patients with inducible ventricular tachycardia who were discharged on drugs considered effective confirms the predictive value of electrophysiologically controlled serial drug testing. Although there have been no studies on the reproducibility of programmed ventricular stimulation in arrhythmogenic right ventricular disease, our results indicate that electrophysiological study and successful serial drug testing may select patients at lower risk of sudden cardiac death. Of the 11 patients with drug-refractory inducible ventricular tachycardia, one patient with multiple origins of right ventricular tachycardia and a progressive and extensive form of arrhythmogenic right ventricular dysplasia died suddenly 3 months after successful repeated catheter ablation.

In patients with noninducible ventricular tachycardia, serial drug testing controlled by Holter monitoring and exercise testing may be sufficiently safe, provided there is no history of life-threatening events. In case of survived cardiac arrest or recurrent syncope and noninducibility of ventricular tachyarrhythmia, the implantation of a cardioverter-defibrillator should be considered.

Recurrences of ventricular tachycardia may not necessarily reduce the reliability of electrophysiologically or Holter controlled serial drug testing because they also may be due to metabolic abnormalities (such as hypokalemia in one of our patients) or progression of the underlying disease. The latter should especially be considered in case of late recurrences during long-term follow-up of arrhythmogenic right ventricular disease.

\textbf{Study Limitations}

To our knowledge, this is the first large-scale report on the effect of various antiarrhythmic drugs in arrhythmogenic right ventricular disease. However, several limitations of the present study should be addressed. The study was a nonrandomized, partly retrospective analysis of drug efficacy. All available information concerning previous antiarrhythmic drug therapy was prospectively documented, but the decision to treat a patient with a given antiarrhythmic drug was based on clinical grounds that were sometimes arbitrary. The data may be biased by the selection of drugs during serial antiarrhythmic testing in our institution since the favorable response to sotalol later resulted in a first-line application of this specific drug in the treatment of patients with arrhythmogenic right ventricular disease. As drug administration was not randomized, this may have influenced the efficacy rates in this study. In addition, there was no standard antiarrhythmic drug dosing, and blood levels usually were not available. Furthermore, most of the patients were referred to our department for further antiarrhythmic treatment of severe symptoms and were preselected to some extent as many had undergone previous antiarrhythmic drug therapy that had failed. With the exception of verapamil, differences between the two patient groups concerning the response rates to antiarrhythmic drugs may be due at least in part to the methods of drug testing used in this study. Patients with inducible ventricular tachycardia were evaluated using the more rigorous method of serial electrophysiologic testing, which may have resulted in lower efficacy rates compared with patients with noninducible ventricular tachycardia in whom drug testing was controlled by repeated Holter and exercise tests.
Clinical Implications

The low recurrence rates of ventricular tachycardia and the absence of sudden death during long-term follow-up of patients after successful serial drug testing indicates the predictive value of electrophysiologically guided serial drug testing in patients with arrhythmogenic right ventricular disease and inducible ventricular tachycardia. In patients with noninducible ventricular tachycardia, serial drug testing guided by repeated Holter and exercise tests may be sufficiently safe, provided there is no history of life-threatening arrhythmias necessitating the implantation of a cardioverter-defibrillator.

Oral sotalol may be a first-line antiarrhythmic agent in the treatment of both inducible and noninducible ventricular tachycardia in patients with arrhythmogenic right ventricular disease. Patients with inducible ventricular tachycardia not responding to sotalol are likely to prove to be drug refractory and may be candidates for early nonpharmacological therapy without extensive serial drug testing. Amiodarone did not prove to be more effective than sotalol and may not be an alternative because of frequent side effects during long-term therapy. β-Blockers and verapamil may be an alternative in the treatment of noninducible ventricular tachycardia in arrhythmogenic right ventricular disease. Class I antiarrhythmic drugs appear to be rarely effective in both inducible and noninducible ventricular tachycardias of right ventricular origin. A prospective randomized study has been started to further elucidate and confirm these results.

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Circulation. 1992;86:29-37
doi: 10.1161/01.CIR.86.1.29

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