The Direct Electrophysiologic Effects of Disopyramide Phosphate in the Transplanted Human Heart


SUMMARY / To evaluate the direct electrophysiologic effects of i.v. disopyramide phosphate and to differentiate these effects from its autonomically mediated actions, we administered the drug (2 mg/kg over 5 minutes) during electrophysiologic study to eight cardiac transplant recipients who had documented functional cardiac denervation.

After disopyramide, the cycle length of the denervated donor right atrium increased from 626 ± 129 to 716 ± 148 msec (mean ± so, p < 0.001), whereas that of the innervated recipient atrium decreased from 846 ± 195 to 659 ± 99 msec (p < 0.02). There were small increases in both the sinus node recovery time (1128 ± 616 to 1198 ± 592 msec, p < 0.05) and corrected sinus node recovery time (440 ± 418 to 489 ± 409 msec, p < 0.02) of the donor atrium, whereas the recovery times of the recipient atrium shortened (sinus node recovery time, 1298 ± 218 to 1218 ± 196 msec; corrected sinus node recovery time, 464 ± 108 to 410 ± 115 msec). Disopyramide markedly prolonged all conduction intervals. The PA interval increased from 47 ± 16 to 54 ± 17 msec (p < 0.01), the AH interval from 55 ± 12 to 78 ± 12 msec (p < 0.001), the HV interval from 38 ± 9 to 58 ± 13 msec (p < 0.001), the QRS duration from 93 ± 10 to 129 ± 34 msec (p < 0.001) and the QT interval from 339 ± 23 to 403 ± 39 msec (p < 0.001). There was no significant change in the effective refractory period of the atrium, ventricle or atrioventricular node. The functional refractory period of the atrioventricular node increased from 369 ± 34 to 395 ± 31 msec (p < 0.001).

The electrophysiologic effects of disopyramide in the denervated heart are markedly depressant. In the innervated normal heart, the majority of these effects are counteracted by the drug’s autonomic mediators anticholinergic actions.

DISOPYRAMIDE phosphate, the antiarrhythmic properties of which were first described in 1962,1 is an effective antiarrhythmic agent in the clinical management of a variety of supraventricular and ventricular arrhythmias.2-10 In vitro, the drug reduces the rate of rise of phase 0 of the action potential and possesses local anesthetic properties.11-14 It is thus primarily a class I agent according to the classification of Vaughan Williams.15 Investigations of disopyramide’s electrophysiologic properties in humans have produced inconsistent and conflicting results16-24 (table 1). These discrepancies reflect the dual mode of action of the drug: its direct membrane depressant effects and its anticholinergic effects, which tend to counteract the direct depressant effects.

There is considerable evidence that the transplanted heart remains anatomically and functionally denervated indefinitely after cardiac transplantation,25,26 providing a unique model for studying the electrophysiologic properties of the heart free of autonomic influences.27-31 However, during clinical cardiac transplantation, the posterior portions of the recipient atria, together with the sinus node, are left in situ23 and remain functionally innervated.32 Cardiac transplant recipients thus provide the ideal model to assess the relative contributions of the two modes of action of disopyramide phosphate.

Patients and Methods

Patients

Eight male orthotopic cardiac transplant recipients, ages 24–54 years (mean 37 years), underwent routine electrophysiologic study 4–28 months (mean 16 months) after transplantation (table 2). The study was performed because of the known high incidence of sinus node and conduction system disease in patients after cardiac transplantation.25,34,35

At the time of the investigation, all patients were functionally well and showed no clinical, biochemical or electrocardiographic evidence of rejection. All eight patients had normal right- and left-heart hemodynamic studies and left ventricular angiograms within 6 months of the investigation.

Two patients had complete right bundle branch block on the resting ECG, but in one of these cases this abnormality had been present on the ECG from the donor before transplantation. All patients were taking prednisolone and azathioprine as routine immunosuppressive therapy at the time of investigation. No patient was taking cardioactive drugs.

Electrophysiologic Study

All patients were studied in the nonsedated, postabsorptive state after they gave written, informed consent. Under local anesthesia and fluoroscopic guidance, five pacing electrodes were introduced into the right femoral vein and positioned in the heart.

As a result of the surgical technique used for human cardiac transplantation,32 the posterior portions of the recipient right and left atria, together with the sinus
node, are left in situ and serve to anchor the donor heart. Each patient thus has two sinus nodes — the innervated recipient sinus node driving only the atrial remnant and the denervated donor sinus node driving the donor atria and ventricles. The two sets of atria beat independently, and both recipient and donor P waves can be recorded electrocardiographically. A similar approach was used from intracardiac electrodes both recipient and donor atrial electrograms can be recorded and the two sets of atria paced independently.

A quadrupole electrode was positioned at the junction of the superior vena cava and the right atrium to record and stimulate the recipient sinus node and atrial remnant. Lateral fluoroscopy was used to confirm the posterior position of this electrode. Two bipolar electrodes were positioned in the appendage of the donor right atrium for recording and stimulation. The anterior location of these electrodes was confirmed radiographically. However, in one of the patients, despite careful mapping of the whole of the posterior wall of the right atrium, no recipient sinus node electrical activity could be detected nor could the atrium be paced.

An electrode was advanced to the right ventricular apex for stimulation and a further electrode was positioned against the septal leaflet of the tricuspid valve to record the His potential. This electrode was adjusted to record distinct low right atrial, His bundle and right ventricular electrograms. In one patient with a persistent foramen ovale, an electrode was also positioned in the left atrium. Intracardiac signals were filtered between 50 and 700 Hz and recorded on a Mingograf ink-jet recorder (Siemens-Elema Schonander) at a paper speed of 100 mm/sec, simultaneously with four surface electrocardiographic leads. Intracardiac stimulation was achieved with a Devices 4279 isolated stimulator (Digitimer Ltd.) that emitted square-wave pulses of 1.5–2.5 msec duration at approximately twice the diastolic threshold.

Conduction intervals were measured during sinus rhythm and during constant rate donor atrial pacing at a cycle length of 500 msec. Antegrade and retrograde conduction characteristics and refractoriness of the heart were determined by introducing an extrastimulus after regular atrial or ventricular pacing at a cycle length of 500 msec. Incremental atrial pacing from the donor right atrium and incremental ventricular pacing were performed to determine the maximal cycle length at which Wenckebach periodicity was present. Standard sinus node function tests were performed. All intervals were measured to the nearest 5 msec.

Disopyramide Administration

After the baseline electrophysiologic evaluation,
i.v. disopyramide (2 mg/kg body weight, maximal dose 150 mg) was administered over 5 minutes. Continuous electrocardiographic recordings were made throughout the infusion and for 5 minutes after its completion. The blood pressure was measured sphygmomanometrically at 3-minute intervals during this period. The postdrug electrophysiologic evaluation was performed 5 minutes after completion of the infusion at identical paced rates and driven cycle lengths.

Definitions

Atrial cycle length (ACL). The average cycle length of 10 consecutive, spontaneous atrial cycles. The ACL was measured for both the donor right atrium and the recipient right atrium.

Sinus node recovery time (SNRT). The maximum sinus pause after the abrupt termination of right atrial pacing at rates of 110, 130, 150 and 170 beats/min for periods of 15, 30 and 60 seconds at each rate, measured from the pacing stimulus to the first high-frequency deflection of the escape sinus beat.39 The results were corrected for the sinus cycle length (cSNRT).40 The SNRT of both the donor and the recipient was assessed.

Sinoatrial conduction time (SACT). SACT was estimated by introducing programmed premature atrial beats during sinus rhythm and calculated according to the revised method of Strauss et al.41 This interval represents the sum total of the conduction time into and out of the sinus node. The SACT was assessed in both the donor and the recipient portions of the heart.

In the transplanted (donor) heart, conduction intervals were measured during sinus rhythm and constant-rate atrial pacing according to previously described definitions.42 The antegrade and retrograde Wenkebach cycle lengths and refractory periods were estimated using standard techniques37,38 and definitions.42

The persistence of functional cardiac denervation was confirmed; on the day before the investigation, all eight patients had shown a delayed heart rate response, in onset and offset, during treadmill exercise testing. Immediately before the electrophysiologic evaluation, various physiologic maneuvers were performed, including carotid sinus massage, cold pressor test and the Valsalva maneuver. In no case was there a change in the donor atrial cycle length, and the recipient atria responded appropriately.

Statistical Analysis

Results are presented as the mean ± SD. The two-tailed t test for paired data was used to determine probable differences, which were considered significant when p < 0.05.

Results

The mean dose of disopyramide was 146 mg (range 130–150 mg). Comparative electrophysiologic data are shown in tables 3, 4 and 5.

Sinus Node Function (table 3)

The donor ACL increased in all patients (from 626

<table>
<thead>
<tr>
<th>Table 3. Effect of Disopyramide on Sinus Node Function</th>
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<tbody>
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<td>ACL (RAD)</td>
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</tr>
<tr>
<td>626 ± 129</td>
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<tr>
<td>846 ± 195</td>
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<td>1128 ± 616</td>
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<tr>
<td>1298 ± 218</td>
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<td>440 ± 418</td>
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<td>464 ± 108</td>
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<td>159 ± 50</td>
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<td>157 ± 35</td>
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All values are expressed in milliseconds as the mean ± SD. *Two-tailed t test for paired data.

Conduction (table 4)

After disopyramide, the PA interval significantly prolonged from 47 ± 16 to 54 ± 17 msec (p < 0.01), as did the SA interval during atrial pacing (from 44 ± 14 to 56 ± 13 msec, p < 0.001). The AH interval prolonged by an average of 44% during sinus rhythm (from 55 ± 12 to 78 ± 12 msec, p < 0.01) and by

<table>
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<th>Table 4. Effect of Disopyramide on Conduction Intervals</th>
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<tr>
<td>Interval</td>
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</tr>
<tr>
<td>PA</td>
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<td>SA (atrial pacing)</td>
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<td>AH</td>
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<td>AH (atrial pacing)</td>
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<td>HV</td>
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<td>QRS duration</td>
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<td>QT</td>
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<td>QTc</td>
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<td>JT (atrial pacing)</td>
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All values are expressed in milliseconds as the mean ± SD. *Two-tailed t test for paired data.
TABLE 5. Effect of Disopyramide on Refractoriness

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Disopyramide</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV Wenck CL</td>
<td>314 ± 22</td>
<td>350 ± 35</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VA Wenck CL</td>
<td>419 ± 108</td>
<td>500 ± 106</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AERP</td>
<td>192 ± 21</td>
<td>198 ± 20</td>
<td>NS</td>
</tr>
<tr>
<td>AVERP</td>
<td>277 ± 21</td>
<td>296 ± 41</td>
<td>NS</td>
</tr>
<tr>
<td>AVFRP</td>
<td>369 ± 34</td>
<td>395 ± 31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VERP</td>
<td>216 ± 16</td>
<td>226 ± 15</td>
<td>NS</td>
</tr>
</tbody>
</table>

All values are expressed in milliseconds as the mean ± SD.

Abbreviations: AV Wenck CL = atrioventricular Weneckbach cycle length; VA Wenck CL = ventriculoatrial Wenckbach cycle length; AERP = atrial effective refractory period. AVERP = atrioventricular ERP; AVFRP = AV functional refractory period; VERP = ventricular ERP.

33% during constant-rate atrial pacing (from 71 ± 8 to 93 ± 9 msec, p < 0.001) (fig. 2). His-Purkinje conduction times (HV) prolonged markedly, from 38 ± 9 to 58 ± 13 msec (p < 0.001) (fig. 2). After disopyramide, the HV interval prolonged in all patients by increments (expressed as a percentage of the control HV interval) of 29–100% (mean 52%).

QRS duration increased from 93 ± 18 to 129 ± 34 msec (p < 0.001) (fig. 3). The maximal increase of 70 msec occurred in one of the patients with preexisting right bundle branch block. The increments in QRS duration expressed as a percentage of the control QRS duration was 24–54% (mean 37%). The QT intervals during sinus rhythm (from 339 ± 23 to 403 ± 39 msec, p < 0.001), constant-rate atrial pacing (from 334 ± 18 to 383 ± 23 msec, p < 0.001) and the corrected QT interval (from 435 ± 28 to 487 ± 26 msec, p < 0.01) lengthened significantly after disopyramide (fig. 3). Although this increase in the QT interval can be partly accounted for by the increase in QRS duration, the JT interval, measured during constant-rate atrial pacing, was also increased significantly (from 242 ± 13 to 274 ± 17 msec, p < 0.001).

In the one patient in whom an electrode was positioned in the left atrium through a persistent foramen ovale, disopyramide increased the interatrial conduction time from 70 to 85 msec. Figure 4 shows typical changes in the conduction intervals after disopyramide.

Refractoriness (table 5)

The antegrade atrioventricular (AV) Wenckebach cycle length prolonged in all patients after disopyramide (from 314 ± 22 to 350 ± 35 msec, p < 0.01) (fig. 5). Retrograde ventriculoatrial (VA) conduction, during ventricular pacing at rates above the donor sinus rate, occurred in only five patients during the control study and in four patients after disopyramide. In these four patients, the retrograde VA Wenckebach cycle length was prolonged after the drug (from 419 ± 108 to 500 ± 106 msec, p < 0.01) (fig. 5).

The effective refractory period of the donor atrium increased slightly (from 192 ± 21 to 198 ± 20 msec; NS). Assessment of the AV nodal effective refractory period was limited by atrial refractoriness in three of the eight patients. No significant change occurred in the remaining five patients (from 277 ± 21 to 296 ± 41 msec). The functional refractory period of the AV node was significantly prolonged by disopyramide (from 369 ± 34 to 395 ± 31 msec, p < 0.001). There was a small but insignificant increase in the effective refractory period of the ventricle (from 216 ± 16 to 226 ± 15 msec). At the pacing cycle length used to estimate the refractory periods (500 msec), only three patients had retrograde VA conduction during ventricular pacing at the time of the control study and only one patient after disopyramide. Hence, the retrograde refractory periods of the AV node could not be assessed.

Disopyramide Levels

Blood for disopyramide levels, collected 10 minutes after drug administration, revealed serum disopyramide levels of 2.3–5.85 μg/ml (mean 4.29 μg/ml).

Side Effects

In no patient was there a change of greater than 5 mm Hg in systolic or diastolic blood pressure, measured during the disopyramide infusion and for the following 5 minutes. No major side effects were experienced and the only minor side effect, experienced by all patients, was dryness of the mouth.

Discussion

In isolated tissue models of atrial and ventricular muscle and Purkinje fibers, disopyramide slows the rate of rise of phase 0, decreases membrane respon-
siveness, increases conduction time, and prolongs the action potential duration and the effective refractory period. These effects should be evidenced clinically, in intact humans, by lengthening of the PR interval, QRS complex and QT interval on the surface ECG and by prolongation of the refractory periods and conduction intervals during electrophysiologic study. Not all of these expected actions, however, have been observed in the majority of reported studies\(^{16-24}\) (table 1), presumably because of the indirect, autonomically mediated effects of disopyramide initially described by Mokler and Van Arman\(^1\) in 1962.

The presence of both an innervated and a denervated sinus node in these patients allows the relative contributions of the direct and the indirect autonomic actions of disopyramide on sinus node automaticity to be assessed. The innervated node significantly increased its rate of discharge, which is in accord with several of the reported studies,\(^{16, 22-24}\) whereas the denervated sinus node was markedly slowed by disopyramide. This finding clearly separates the direct effect of the drug, depressing sinus node automaticity, from its anticholinergic accelerative effect. Marrott et al.\(^{19}\) stated that with a similar dosage regimen the anticholinergic effects of disopyramide are probably minimal, but our results indicate that the drug’s predominant effect on the innervated “normal” sinus node is autonomically mediated and that this effect considerably outweighs the direct depressant effect.

This finding is confirmed by disopyramide’s similar effect on the SNRTs. The SNRT of the denervated node increased significantly, whereas the SNRT of the innervated sinus node shortened, although not significantly, as previously described in normal subjects.\(^{17, 24, 43}\) Disopyramide has been reported to increase sinus node recovery times in patients with sinus node dysfunction.\(^{23, 24, 43}\) In such patients the response to anticholinergic drugs is unpredictable and the direct depressant effect of disopyramide may predominate.

The effect of disopyramide on the conduction intervals in the denervated heart was universally and markedly depressant. Although previous studies in animals\(^{14, 44-46}\) have shown dose-related increases in AV nodal conduction time, studies in intact humans have

**Figure 2.** Effect of disopyramide on the AH interval (measured during sinus rhythm and constant rate atrial pacing) and the HV interval.

**Figure 3.** Effect of disopyramide on QRS duration and QT interval (measured during sinus rhythm constant rate atrial pacing) corrected for heart rate (QTc).
shown no change in the AH interval after disopyramide. In the denervated heart, disopyramide markedly depresses AV nodal conduction, as evidenced by increases in the AH interval and Wenckebach cycle lengths, indicating that in "normal subjects" the anticholinergic effect of the drug usually counteracts its direct depressant effect on the AV node. Similarly, disopyramide has had an inconsistent effect on the HV interval and QRS duration. In patients with a normal HV interval, the drug reportedly has either no effect on the HV interval or increases it. In other studies, disopyramide increased the HV interval only in patients who had abnormally prolonged HV intervals before administration of the drug. The reason for these discrepancies is unclear and does not appear to be related to the dosage regimen used. In the transplanted heart, both the HV interval and QRS duration were markedly prolonged, which perhaps indicates that because of previous rejection episodes or surgery, the His-Purkinje system and ventricular myocardium of the transplanted heart are particularly susceptible to such an intervention. Although the effect of disopyramide on the His-Purkinje system appears to be directly mediated, the possibility exists that autonomic effects may influence the response in normal subjects, for the His-Purkinje system has been demonstrated histologically to have cholinergic innervation. However, studies in intact man have shown that neither anticholinergic drugs such as atropine nor cholinergic drugs such as edrophonium affect the HV interval. Both the QT and JT intervals were prolonged in this study, which is in accord with previous reports although the increases were more marked. Anticholinergic drugs shorten the QT interval, which explains the more marked effect of disopyramide in the transplanted heart.

In normal patients, the only consistent effect of disopyramide on refractoriness is an increased atrial effective refractory period. Thus, we were surprised to find only a small, nonsignificant increase in atrial refractoriness. In a similar study on the effect of quinidine in transplant recipients, Mason et al. concluded that the increase in atrial refractoriness in intact man after quinidine was due to a direct drug effect and an anticholinergic effect acting in concert. However, several reports have indicated that atropine either shortens or has no effect on atrial refractoriness, which suggests that the effect of disopyramide on atrial refractoriness in the transplanted heart should be more marked than in the innervated heart. The reason for our discrepant results is not clear.

In the intact patient, disopyramide either shortens or has no effect on the effective refractory period of the AV node and either lengthens slightly or has no effect on the functional refractory period (table 1). In this study both variables, particularly the functional refractory period, were lengthened by the drug. Thus, in the normal heart the anticholinergic effects of disopyramide, tending to shorten AV nodal refractoriness, preclude the direct effect. The more marked effect on the AV nodal functional refractory period is probably due to the increased AH conduction time induced by disopyramide.
refractoriness tended to increase, as reported in the innervated human heart.\textsuperscript{18,22}

In this study, we found a clear separation of disopyramide’s directly mediated actions from its autonomic effects. Our results confirm and further extend the results of Birkhead and Vaughan Williams,\textsuperscript{21} who studied patients given atropine, and those of Dreifus,\textsuperscript{26} who administered disopyramide to rabbits with denervated hearts. The results suggest that in the absence of cholinergic innervation, disopyramide exerts markedly depressant effects upon the cardiac conduction system in man. The variable results previously reported can be explained by the interaction of these direct depressant effects and the anticholinergic properties of the drug. In the intact innervated heart, the drug’s effects on the sinoatrial and AV nodes are largely autonomically mediated, whereas the drug’s effects on the His-Purkinje system, ventricular myocardium and on repolarization are predominantly directly mediated, as would be predicted from the extent of cholinergic innervation of these various components of the conduction system.

References
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34. Schroeder JS, Berke AK, Graham AF, Rider AK, Harrison DC: Arrhythmias after cardiac transplantation. Am J Cardiol 33: 604, 1974

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AMIODARONE has been available in Europe for approximately 20 years for the management of angina pectoris, but only in the past decade have its unique antiarrhythmic properties been recognized. It is effective in the management of refractory ventricular arrhythmias, including those associated with ischemic heart disease and the cardiomyopathies. It is particularly useful in the management of chronic atrial arrhythmias refractory to conventional drugs, with an impressive conversion rate of chronic atrial fibrillation to sinus rhythm. Amiodarone is especially effective in suppressing or modifying paroxysmal atrial arrhythmias, including those associated with the Wolff-Parkinson-White syndrome, in which sudden death from rapidly conducted atrial fibrillation is a risk.

With the more widespread use of amiodarone, several side effects have been identified. In the majority of patients, these are well tolerated and are often modified by a reduction in dosage so that discontinuation of therapy is rarely necessary. A few patients, however, have more serious complications, including pulmonary fibrosis and clinical thyroid disease. The incidence, mechanisms and management of these complications is uncertain. Our experience in individual cases dates back over 9 years. We are now able to report 140 patients in whom we have systematically monitored the unwanted effects over the past 5 years.

**Patients and Dosage**

We reviewed 140 patients (95 males and 45 females, mean age 52 years) who had been taking amiodarone for an average of 2 years; the longest follow-up was 5 years. Although 69 of our patients were taking amiodarone for primary arrhythmias, including the Wolff-Parkinson-White syndrome, we also treated 15 patients with ischemic heart disease and 48 who had arrhythmias associated with cardiomyopathy, 28 hypertrophic and 20 congestive. Five patients had valvular disease, two hypertensive heart disease and one patient an atrial septal defect. Details of the arrhythmias treated are listed in table 1.

The dose varied from 100 to 1200 mg/day, but only 11 patients took 600 mg/day or more long-term; the...
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R S Bexton, K J Hellestrand, R Cory-Pearce, R A Spurrell, T A English and A J Camm

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