Effect of Oral Disopyramide Therapy on Left Ventricular Function

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To study the effect of oral disopyramide therapy on left ventricular function, a subject of some controversy, we obtained first-pass radionuclide ventriculograms with a multicrystal gamma camera in 19 patients with or without therapy. Our findings demonstrated that disopyramide causes deterioration in left ventricular function in patients with abnormal ejection fractions. This effect is rarely recognized clinically and occurs despite safe therapeutic serum levels.

Disopyramide (Norpace) is an effective type 1 antiarrhythmic agent for the treatment of atrial and ventricular arrhythmias. Its modes of action include depression of conduction velocity and automaticity and augmentation of atrial and ventricular refractoriness.1,4 The common side effects are related to the anticholinergic actions of the drug, such as dry mouth and urinary retention. Disopyramide has recently been implicated in the causation or exacerbation of congestive heart failure in certain patients, particularly those with overt heart failure or a history of heart failure.3,8 However, few studies reported in abstracts only have provided objective assessment of left ventricular function by radionuclide ventriculography. Furthermore, these investigators have reached conflicting conclusions.6,7 Therefore, the purpose of this prospective study was to evaluate the effects of disopyramide on rest and exercise left ventricular performance.

Materials and Methods

Patient Population

The study group consisted of 19 patients (13 men and six women) with a mean age of 55.8 years (range 42 to 71). Eleven patients had ischemic heart disease (proved by coronary angiography or by history and ECG evidence of prior myocardial infarction); two patients had mitral regurgitation; one patient had hypertrophic cardiomyopathy; and five patients had arrhythmias but no known organic heart disease.

Among the 11 patients with coronary artery disease, the resting ejection fraction was normal (>50 percent) in three, and abnormal in eight patients (between 30 and 49 percent in four patients and <30 percent in the remaining four patients). The wall motion was normal in the three patients with normal ejection fraction, showed hypokinesis in the four patients with mild-to-moderate left ventricular dysfunction, and showed akinesia or dyskinesis in one or more segments in the patients with severe dysfunction (ejection fraction <30 percent). Seven of the 11 patients were receiving propranolol for control of angina pectoris.

The indications for treatment, as determined by the treating physicians, were symptomatic ventricular arrhythmias in 17 patients and symptomatic atrial arrhythmias in two patients. All patients were in sinus rhythm. Two patients had a past history of congestive heart failure. None of the patients in this study had experienced recent myocardial infarction (within three months), unstable angina pectoris, severe heart failure, uncontrolled hypotension or hypertension, atrial fibrillation, glaucoma, urinary retention, or severe renal failure.

Study Protocol

Seven of the 19 patients underwent symptom-limited upright exercise before treatment with disopyramide. Radionuclide ventriculograms were obtained at rest and during peak exercise. Ten additional patients had only resting radionuclide ventriculograms before treatment. After the control studies were obtained, disopyramide, 150 mg every six hours (range 100 to 300 mg four times a day), was given for seven days. The dose was adjusted according to body size, renal function, and the nature of the arrhythmia being treated. On the seventh day of treatment, the seven patients who had previously undergone exercise studies underwent a second exercise study, during which rest and exercise radionuclide ventriculograms were obtained. In ten other patients, rest studies were done before, and seven days after, treatment with disopyramide. The total disopyramide serum levels were obtained two to three hours after the last dose by gas chromatography (Upjohn Laboratory; therapeutic range 2 to 4 µg/ml) at the time of the second rest or rest/exercise studies. Beta blockers remained unchanged after the initiation of disopyramide therapy. None of the patients was taking digoxin.

In the remaining two patients, rest radionuclide ventriculograms were obtained while the patients were being treated with disopyramide. These two patients had been receiving disopyramide (150 mg every six hours) for six months and were in a compensated state of congestive heart failure. Serum levels of disopyramide were obtained simultaneously with the radionuclide ventriculograms. In these two patients, disopyramide was subsequently discontinued, and radionuclide ventriculograms were repeated at rest ten days later; no other medication adjustments were made. The only reason for discontinuation of disopyramide therapy was to ascertain the drug effect on left ventricular function. These two patients, therefore, were not the same patients in whom overt heart failure was diagnosed after the initiation of treatment.

Exercise Testing

All exercise studies were performed with the patient upright on a variable-load bicycle ergometer (Quinton Instruments). The workload of exercise was increased by 100 kpm/min every two minutes.
until the end-points of exercise. Two ECC leads, CM5 and aVF, were constantly monitored during testing, and blood pressure was measured by the cuff method every minute. The test was stopped when any of the following criteria were met: (1) severe fatigue, leg weakness, or shortness of breath; (2) hypotension or dizziness; (3) severe angina pectoris; (4) 2 mm or more ST segment depression, with or without angina pectoris; (5) ventricular tachycardia or frequent ventricular premature beats; (6) achievement of at least 85 percent of the predicted maximal heart rate. All patients completed exercise studies without complications.

Radionuclide Ventriculography

All first-pass radionuclide ventriculograms were obtained with a computerized multicrystal gamma camera (Baird-Atomic Systems-77) equipped with a one-inch parallel-hole collimator positioned anterior to the precordium. We inserted a 90-gauge polyethylene catheter into a large basilic vein and rapidly administered a 15-mCi dose of 99m technetium pertechnetate dissolved in a volume of less than 1 ml, after which 20 ml of normal saline solution was injected. Precordial counts were recorded at frame intervals of 50 ms for the rest studies and 25 ms for the exercise studies during the initial pass of the radionuclide through the central circulation. The technique has been previously described.1,6

The radionuclide angiograms were analyzed with computer software incorporated into the multicrystal camera.6,11,12 Left ventricular ejection fraction was determined from the background-corrected representative cardiac cycle as follows:

\[
\text{End-diastolic counts} - \text{end-systolic counts} \times \frac{100}{\text{End-diastolic counts}}
\]

End-diastolic counts

Left ventricular end-diastolic volume was calculated by the arealength method of Dodge et al12 for the ellipse of revolution modified for the single anterior plane projection as \(0.95 \times A^2 L\), where \(A\) is the area obtained by planimetry and \(L\) is the longest diameter measured from the aortic valve to the apex of the left ventricle.

The stroke volume and cardiac output were derived from the measured ejection fraction, end-diastolic volume, and heart rate by the following equations:

\[
\text{Stroke volume (ml)} = \text{end-diastolic volume (ml)} \times \text{ejection fraction (\%)}
\]

\[
\text{End-diastolic volume (ml)} = \text{stroke volume (ml)} - \text{end-systolic volume (ml)}
\]

\[
\text{Cardiac output (liters per minute)} = \text{stroke volume (ml)} \times \text{heart rate (beats per minute)}/1000
\]

We have found that measurement of the left ventricular ejection fraction is accurate when compared with contrast angiography \((r = 0.93)\) and is reproducible when sequential studies are performed \((r = 0.98)\). In another study,6 we have shown specifically that in patients with depressed left ventricular ejection fraction, the reproducibility of radionuclide angiography is excellent; the maximum difference between sequential studies is 5 percent (absolute units). Similarly, we have found that measurement of the end-diastolic volume correlated with contrast angiography \((r = 0.94)\) and was reproducible \((r = 0.95)\).

In this laboratory, we have found that in normal subjects, the resting ejection fraction is \(\geq 50\) percent, and thus, if the ejection fraction is \(< 50\) percent, it is considered abnormal. Also, a failure to increase the ejection fraction \(> 5\) percent during exercise is considered to indicate an abnormal response.6,13

Statistical Analysis: The paired Student's t-test was used to compare differences in individual measurements at rest and during exercise in each group. Significance of differences between groups was obtained using the unpaired t-test. A probability \((p)\) value of \(\leq 0.05\) was considered significant. Results are expressed as the mean ± the standard deviation (SD) when appropriate.

RESULTS

The resting left ventricular ejection fraction off disopyramide therapy was \(\geq 50\) percent in seven patients and \(< 50\) percent in 12 patients.

Heart Rate and Blood Pressure

There was no significant difference attributable to disopyramide in resting heart rate or blood pressure in patients with normal or abnormal baseline left ventricular function. The mean resting heart rate before and after disopyramide therapy in the patients with normal left ventricular function was 73 ± 13 and 75 ± 18 beats per minute respectively \((p = \text{NS})\). The heart rate in patients with abnormal left ventricular function before and after disopyramide therapy was 74 ± 15 and 70 ± 16, respectively \((p = \text{NS})\). Similarly, resting systolic blood pressure in patients with normal ejection fraction was 122 ± 21 mm Hg before disopyramide therapy and 122 ± 19 mm Hg after therapy.

\[
\begin{align*}
\text{Figure 1. Left ventricular ejection fraction (EF) before (C) and after disopyramide (D) therapy. Panel A} & \text{ shows the results in patients with abnormal baseline EF, panel B shows the results in patients with normal baseline EF.}
\end{align*}
\]
(p = NS). In patients with abnormal ejection fractions, resting systolic blood pressure before and after therapy was 133 ± 17 and 134 ± 20 mm Hg, respectively (p = NS).

**Left Ventricular Ejection Fraction**

The resting left ventricular ejection fraction was significantly influenced by disopyramide therapy in patients with abnormal baseline function but not in patients with normal baseline function. The resting left ventricular ejection fraction in our patients with abnormal function before therapy was 34 ± 10 percent; it decreased to 29 ± 11 percent after therapy, (p<0.001) (Fig 1). On the other hand, in patients with ejection fraction ≥ 50 percent, the ejection fraction before disopyramide therapy was 59 ± 6 percent; after therapy it was 60 ± 9 percent (p = NS).

In patients with normal resting ejection fraction, only one of the seven patients had > 5 percent (limit of reproducibility) decrease in ejection fraction while receiving disopyramide. In patients with abnormal resting ejection fraction, five of 12 patients had ≤ 5 percent decrease, and six of 12 patients (50 percent) had > 5 percent decrease in ejection fraction while receiving therapy.

Depression of the ejection fraction was associated with global deterioration of wall motion and was not restricted to the segment with the worse wall motion. As indicated earlier, seven patients with coronary artery disease were receiving propranolol therapy. The change in ejection fraction with treatment was < 5 percent in the three patients with normal ejection fraction and in two of the four patients with abnormal ejection fraction. In the remaining two patients, the decrease was > 5 percent.

Overt heart failure was observed in two patients during therapy. In one patient, the ejection fraction decreased from 16 percent to 11 percent, and in the second patient, it decreased from 18 percent to 14 percent. The serum disopyramide level in these two patients was 4.2 and 2.8 μg/ml, respectively. Both patients showed improvement in congestive heart failure after cessation of therapy.

All other patients were followed for at least one month while receiving therapy, and no other patient developed overt heart failure.

**Effect of Disopyramide on Left Ventricular Volumes and Cardiac Output**

Disopyramide caused a significant decrease in cardiac output in patients with abnormal resting left ventricular function. The cardiac output before therapy in these patients was 3.5 ± 1.1 L/min and after therapy was 2.8 ± 0.9 L/min (p<0.01). However, in patients with normal baseline ejection fractions, cardiac output was not significantly altered; thus, before treatment, the cardiac output was 4.9 ± 2.9 L/min, and after treatment it was 4.1 ± 1.2 L/min (p<0.01).

In patients with normal ejection fractions, the end-diastolic volume before therapy was 190 ± 82 ml and 161 ± 40 ml after therapy (p = NS). The end-systolic volume before therapy in patients with normal ejection fractions was 78 ± 35 ml and was 65 ± 25 ml after therapy (p = NS). In patients with abnormal ejection fractions, the mean (± SD) end-systolic volume was 180 ± 69 ml before therapy and increased slightly but insignificantly (190 ± 56 ml) after therapy (p = NS). The end-systolic volume increased in the six patients showing > 5 percent decrease in ejection fraction with therapy.

**Exercise Studies**

Exercise studies were obtained in seven patients before and during treatments. The resting ejection fraction was normal in five of the seven patients before treatments. In these five patients, the change in resting ejection fraction during treatment was < 5 percent in three patients (patients 1, 2, and 3), and in the remaining two patients (patients 4 and 5), the resting ejection fraction increased during treatment (63 percent vs 73 percent and 62 percent vs 73 percent, respectively) (Table 2).

Only one of the five patients (patient 3) had abnormal ejection fraction response to exercise before treatment (< 5 percent increase). With treatment, three of the five patients had < 5 percent increase in ejection response during exercise including the patient who had an abnormal response before treatment. However, it should be noted that the remaining two patients who had abnormal response to exercise during treatment had resting hyperkinesis (resting ejection fraction > 70 percent), and thus it is not clear whether the failure to

| Table 1—Disopyramide Effects on Resting Left Ventricular Performance* |
|------------------------|------------------------|--------|
|                      | Control                | Disopyramide | p Value |
| Patients with normal EF (n = 7) |                      |                |        |
| HR                    | 73 ± 13                | 75 ± 18            | NS     |
| SBP                   | 122 ± 21               | 122 ± 19           | NS     |
| EDV                   | 190 ± 82               | 161 ± 40           | NS     |
| ESV                   | 78 ± 38                | 65 ± 25            | NS     |
| EF                    | 59 ± 6                 | 60 ± 9             | NS     |
| CO                    | 4.9 ± 2.9              | 4.1 ± 1.2          | NS     |
| Patients with abnormal EF (n = 12) |                      |                |        |
| HR                    | 74 ± 15                | 70 ± 16            | NS     |
| SBP                   | 133 ± 17               | 134 ± 20           | NS     |
| EDV                   | 265 ± 67               | 265 ± 42           | NS     |
| ESV                   | 180 ± 69               | 190 ± 56           | NS     |
| EF                    | 34 ± 10                | 29 ± 11            | p<0.001|
| CO                    | 3.5 ± 1.1              | 2.8 ± 0.9          | p<0.01 |

*Abbreviations are as follows: EF, ejection fraction (%); n, number; HR, heart rate (beats/min); SBF, systolic blood pressure (mm Hg); EDV, end-diastolic volume (ml); ESV, end-systolic volume (ml); and CO, cardiac output (L/min).
Table 2—Exercise Data in Seven Patients*

<table>
<thead>
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<th>Patient</th>
<th>Therapy Code</th>
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<th>Exercise</th>
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<tr>
<td>Patients with normal ejection fraction (n = 5)</td>
<td></td>
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<td>1</td>
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<tr>
<td>5</td>
<td>C</td>
<td>62</td>
<td>79</td>
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<tr>
<td>Patients with abnormal ejection fraction (n = 2)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>C</td>
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</tr>
<tr>
<td>7</td>
<td>C</td>
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*C indicates control, and D, disopyramide.

increase the ejection fraction by 5 percent could be considered drug-induced depression of left ventricular function.

In the remaining two of the seven patients (patients 6 and 7, Table 2) who underwent exercise testing, the resting ejection fraction was <50 percent (43 percent and 34 percent). The resting ejection fraction decreased with treatment to 37 percent and 23 percent, respectively, and the exercise response was abnormal before and after treatment in both patients.

The exercise heart rate was not significantly different before and during treatment in the seven patients (136 ± 24 and 132 ± 24 beats/min, respectively [p = NS]); similarly, the exercise systolic blood pressure was not different (172 ± 18 mm Hg before vs 176 ± 18 mm Hg after treatment [p = NS]).

Correlation Between Effect of Disopyramide and Serum Levels

The serum level of total disopyramide was between 2 and 4 µg/ml in 13 of the 19 patients (65 percent). The change in resting left ventricular ejection fraction with disopyramide therapy did not correlate with the serum level of disopyramide (r = −0.37; p = NS) (Fig 2) or with the baseline ejection fraction.

Discussion

The effects of disopyramide on left ventricular function depend on the route of administration as well as the baseline left ventricular function. A dose-dependent decrease in contractility was observed when disopyramide was administered to animals. In humans, disopyramide, 2 mg/kg of body weight, given intravenously for five minutes, produced a decrease in cardiac output by 7 percent in ten patients with normal left ventricular function. On the other hand, the same dose administered intravenously to patients with left ventricular dysfunction has been shown to produce a depression in resting cardiac output of 16 percent to 18 percent accompanied by a decrease in systolic blood pressure, an increase in pulmonary artery pressure, and a decrease in coronary blood flow. Podrid et al reported that 55 percent of patients with a history of congestive heart failure showed exacerbation of heart failure, usually within three weeks after the start of therapy. However, only 5 percent of patients without prior failure developed heart failure with disopyramide therapy. Several studies have suggested that disopyramide may cause exacerbation of congestive heart failure or even produce cardiogenic shock. Most of the patients in these studies, however, had overt, often severe congestive heart failure, with variable degrees of renal dysfunction; in addition, they had rather high serum levels of disopyramide. None of these studies adequately evaluated disopyramide-induced changes in left ventricular function by means of objective criteria.

Two studies, which have appeared as abstracts, have evaluated changes in left ventricular function with radionuclide ventriculography. Gottdiener et al found that disopyramide, given orally, 150 mg every six hours (serum level 2.5 ± 0.3 µg/ml), did not change resting or exercise ejection fraction either in patients with normal or abnormal left ventricular function. Nevertheless, in 12 patients, a single oral loading dose of 300 mg of disopyramide which resulted in a serum level of 3.5 ± 0.4 µg/ml significantly depressed left ventricular function in all patients. Kowey et al used a similar technique, a loading dose of 300 mg of disopyramide, which resulted in a serum level of 3.2 to 3.6 µg/ml. They confirmed the finding of depressed left ventricular function in patients with abnormal ejection fractions. Neither of these two studies provided clinical correlates with regard to disopyramide-induced left ventricular dysfunction or the effects of the drug on left ventricular volume and cardiac output.

In this study, we found that orally administered disopyramide, 150 mg every six hours, given for an average period of seven days, resulted in significantly depressed resting left ventricular function in patients with preexisting left ventricular dysfunction. Left ventricular ejection fraction decreased from 34 ±10 percent to 29 ±11 percent; (p<0.001) (Fig 1) and cardiac output decreased from 3.5 ±1.1 to 2.8 ±0.9 L/min (p<0.01).

Conversely, patients with resting ejection fraction ≥50 percent did not demonstrate significant changes in ejection fraction and cardiac output with therapy. In six of the 12 patients with abnormal resting ejection fraction, and in one of the seven patients with normal resting ejection fraction, the ejection fraction decreased >5 percent during treatment. In these pa-
patients, the end-systolic volume increased during treatment although the mean end-systolic and end-diastolic volumes did not change with treatment. The serum levels of disopyramide were in the therapeutic range of 2 to 4 μg/ml in 13 of the 19 patients. We also found no correlation between the change in ejection fraction and serum disopyramide levels (Fig 2). It is unclear, however, whether the total level of serum disopyramide, which includes the protein bound and free disopyramide, or the free disopyramide level is the key factor in producing left ventricular depression.16,19 This and other available studies have utilized the serum level of total disopyramide.3-7 We also found no correlation between the degree of change in ejection fraction and the resting ejection fraction.

Among the seven patients who underwent upright exercise, an abnormal ejection fraction response to exercise was found in five patients after treatment and in three before treatment. In the two patients with abnormal response after treatment, the drug could not be definitely incriminated because of the high resting ejection fraction (>70 percent).

Despite significant depression of left ventricular function in patients with abnormal resting ejection fraction, only two patients showed signs and symptoms of congestive heart failure and had very low resting ejection fractions (18 percent and 16 percent). The serum levels of disopyramide in these two patients were 4.2 and 2.8 μg/ml, respectively.

Clinical Implications

Disopyramide in the recommended dosages causes a significant depression of resting left ventricular ejection fraction in patients with abnormal baseline left ventricular ejection fractions. This depression of function appears to occur despite normal serum therapeutic levels. Even with depression of the resting ejection fraction, clinically detectable heart failure is unusual. Radionuclide angiography at rest should probably be obtained before any patient with heart disease begins therapy. A pretreatment ejection fraction is helpful in excluding high risk patients from therapy (those with very low ejection fractions) or in alerting the physician that careful clinical follow-up is warranted.

REFERENCES

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