Clinical Superiority of a New Nonionic Contrast Agent (Iopamidol) for Cardiac Angiography

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The hemodynamic and electrophysiologic alterations induced by ionic contrast agents during cardiac angiography are well described. Recently nonionic contrast agents have become available for cardiac angiography. To evaluate the safety of these new agents, a double-blind randomized study was performed comparing a new nonionic agent (iopamidol) with a commonly used ionic contrast agent (Renografin-76). Eighty-one patients undergoing left ventriculography and coronary angiography were included; 41 received iopamidol and 40 received sodium meglumine diatrizoate (Renografin-76).

After left ventriculography, there was a decrease in the arterial pressure with both contrast agents. However, the severity and duration of hypotension were both significantly greater with Renografin-76 compared with the new nonionic agent (p < 0.001). After selective injections of the coronary arteries, electrocardiographic analysis demonstrated that the increase in the QT interval (p < 0.0002) and the changes in both the ST segment and T wave amplitude (p < 0.001) were significantly greater in the Renografin-76 group compared with the iopamidol group. During coronary angiography, 8 of the 40 patients receiving Renografin-76 required temporary pacing for sinus pauses of 2.5 seconds or more, and 2 of the 40 also developed ventricular fibrillation. None of the 41 patients receiving iopamidol had these complications.

This report demonstrates that the electrocardiographic changes, the severity and duration of hypotension and the incidence of serious arrhythmias are significantly greater with Renografin-76 than with iopamidol. Thus, this new nonionic agent appears to enhance the safety of cardiac angiography.

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Numerous animal and human studies (1–18) have documented the deleterious effects of ionic contrast media on the myocardium immediately after contrast ventriculography and coronary angiography. Decreases in systemic arterial pressure and myocardial contractility and alterations in the ventricular pressure-volume relation after the use of ionic contrast agents are well described (1,4–15). Although the intensity and duration of these changes are known, the mechanisms responsible for these alterations of myocardial function remain controversial. The contribution of various factors, such as contrast-induced hypocalcemia, osmolality of the agent or a direct effect of the contrast molecule or anion, to these hemodynamic and physiologic alterations is unclear (5,7,11–13,15,19–27).

Sodium meglumine diatrizoate (Renografin-76) is a commonly used contrast agent for cardiac angiography. Several studies (1,8,15,17,20) have demonstrated the adverse effects of this standard ionic agent on myocardial function, metabolism and electrophysiology. Metrizamide was the first commercially available nonionic contrast agent. Animal and human studies (15,20,28–32) demonstrated that its adverse hemodynamic and physiologic effects were significantly less than those of ionic agents. In addition, it reduced the discomfort experienced by the patient during intravascular angiography (32). However, metrizamide is unstable in aqueous solution; therefore, it must be reconstituted from the lyophilized form immediately before intravascular injection. Recently, nonionic contrast agents that are hydrolytically stable have been developed and are being evaluated for use in coronary angiography (33–40).

The purpose of this investigation was to evaluate one of these new nonionic agents, iopamidol, in human subjects in a randomized double-blind study. The electrocardio-
graphic and hemodynamic alterations induced by this new agent during left ventriculography and selective coronary angiography were measured and compared with those induced by Renografin-76.

Methods

Patient selection. All patients undergoing left ventriculography and selective coronary angiography at the San Francisco Veterans Administration Medical Center were eligible for this study except for 1) patients with a history of adverse reactions to contrast media or iodine compounds, 2) patients with bleeding disorders, 3) patients with creatinine clearance below 25 ml/min, and 4) patients receiving intravascular or orally absorbable contrast material within 1 week of the study.

The study was of a randomized double-blind design for comparison of iopamidol and sodium meglumine diatrizoate (Renografin-76) as the contrast agent used for left ventriculography and selective coronary angiography. Iopamidol and Renografin-76 both contain 37% iodine. The viscosities of iopamidol and Renografin-76 are similar at 37°C, 9.4 cp and 8.4 cp, respectively.

Procedure. All patients received oral diazepam (10 mg) as premedication. No medications were withheld before the catheterization. No patient received atropine. Electrocardiographic leads I and II were monitored continuously during the procedure. An 8F USCI sheath was placed in the femoral artery. For the treatment of bradyarrhythmias or complete heart block which may develop during coronary angiography, a temporary pacing catheter was inserted through a femoral venous sheath and positioned at the apex of the right ventricle. For asystolic episodes lasting 2.5 seconds or more, pacing was performed at 60 beats/min until the patient's intrinsic rhythm returned. The left ventriculogram was performed using a 7F Cordis high flow pigtail catheter; 0.5 ml/kg of contrast medium was injected at 12 ml/s. The amount of contrast agent injected for the left ventriculogram was 40.5 ± 5.7 ml in the iopamidol group and 37.4 ± 4.9 ml in the Renografin-76 group. Left ventricular volumes and ejection fraction were calculated using a calibrated grid and the method of Kennedy et al. (41). The electrocardiogram, left ventricular pressure and femoral artery pressure were recorded continuously for 6 seconds before the left ventriculogram and for the first 2 minutes after the injection. In all patients, the left ventriculogram preceded the selective injections of the right and left coronary arteries. Similarly, the electrocardiogram and aortic pressure were recorded before and for the first 2 minutes after the first selective injection of the right and left coronary arteries. All recordings were made at a strip chart speed of 100 mm/s. There were no test injections of contrast agent preceding the left ventriculogram or the first selective injection of the coronary arteries. Immediately after the procedure, each patient was asked to grade on a 0 to 10 scale subjective feelings of pain and warmth that occurred during and after the contrast injections.

The cineangiograms were reviewed by an independent observer with regard to quality of contrast, definition and opacification of coronary vessels and were graded as poor, adequate, good or excellent.

Blood for determination of urea nitrogen and serum creatinine was obtained at baseline (before angiography) and at 24 and 48 hours after the procedure. If the values were abnormal at 48 hours, these tests were repeated 1 week after angiography and, if abnormal, repeated until the values returned to baseline levels. The protocol was approved by the Human Research Committees of the University of California and the Veterans Administration Medical Center at San Francisco. Informed written consent was obtained from each patient.

Statistics. All hemodynamic and electrocardiographic variables were analyzed by repeated measures analysis of variance using Tukey's tests to determine whether there was a difference between the changes induced by the two contrast agents (42). The unpaired t test was used to determine whether there was a difference between the hemodynamic and electrocardiographic variables of the iopamidol and Renografin-76 groups at baseline. The chi-square test was used to compare discrete variables. The nonparametric variables such as cineangiographic quality and subjective response of the patients to the contrast agent were compared using the Mann-Whitney test. The data in the text and tables are presented as mean ± 1 standard deviation. The mean values ± 1 standard error are shown in the figures.

Results

Patient characteristics. The study group consisted of 81 male patients. Seventy-nine patients underwent left ventriculography and selective coronary angiography for symptoms of ischemic heart disease and two underwent the procedure for evaluation of valvular heart disease. Forty-one patients received iopamidol and 40 received Renografin-76.

The patient characteristics in these two groups are listed in Table 1. A coronary lesion was considered significant if 75% or more of the cross-sectional luminal area of the vessel was obstructed. There was no significant difference between the two groups in the number of patients with significant left main lesions and with no, one, two or three vessel disease. Two patients receiving Renografin-76 had aortic valve disease; one had significant aortic regurgitation requiring valve replacement and the other had mild aortic stenosis. One patient in the iopamidol group had significant aortic stenosis requiring valve replacement. In each group, there was one patient with mild mitral regurgitation.

Indexes of left ventricular function are also listed in Table 1. There was no significance difference in ejection fraction,
left ventricular end-diastolic volume index and baseline left ventricular end-diastolic pressure between the two groups.

The medications received by the patients before the angiographic study are listed in Table 2. There was no significant difference in the types of medications prescribed for the patients in the two groups.

The baseline (before contrast medium) systolic arterial pressure, left ventricular end-diastolic pressure and electrocardiographic data for these two groups of patients are given in Table 3. There was no significant difference in any of these measurements at baseline between the two groups.

**Hemodynamic alterations.** The baseline (before contrast medium) systolic arterial pressure was 146 ± 22 mm Hg in the Renografin-76 group and 141 ± 24 mm Hg in the iopamidol group (p = NS). After left ventriculography, there was a decrease in the arterial pressure in both groups (Fig. 1). The average decrease in systolic pressure was 48 ± 14 mm Hg in the Renografin-76 group and 19 ± 11 mm Hg in the iopamidol group (p < 0.001). The duration of the decrease in systolic pressure (decrease in systolic pressure >10% of control) was 45 ± 25 seconds in the Renografin-76 group compared with 9 ± 10 seconds in the iopamidol group (p < 0.001). Thus, not only was the decrease in arterial pressure greater after Renografin-76 but also the duration of these changes was significantly longer compared with iopamidol. The change in left ventricular end-diastolic pressure induced by ventriculography is also shown in Figure 1. After injection of Renografin-76, the average increase in end-diastolic pressure at 90 seconds after the ventriculogram was 9 ± 7 mm Hg compared with 1 ± 5 mm Hg for iopamidol. This difference was highly significant (p < 0.001).

The systolic arterial pressure during the control period and after the first selective injection of the right and left coronary arteries is shown in Figure 2. There was no significant difference between the two groups in the arterial pressure during the control period. After selective injection of either the right or the left coronary artery, arterial pressure did not change in the iopamidol group but decreased significantly in the Renografin-76 group (p < 0.001).

**Electrocardiographic changes.** Figure 3 compares the electrocardiographic changes induced by selective contrast injections of the left and right coronary arteries and left ventriculography in the Renografin-76 and iopamidol groups. Data are shown for the control period and for the 60 second period after the contrast injection. With selective left coronary injection, there was a marked prolongation of the QT interval, from 394 ± 32 to 482 ± 56 ms, in the Renografin-76 group (p < 0.001), but only a slight increase, from 386 ± 33 to 393 ± 36 ms, in the iopamidol group (p = NS). A repeated measures analysis of variance showed that there

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**Table 1. Characteristics of Patients**

<table>
<thead>
<tr>
<th></th>
<th>Iopamidol</th>
<th>Renografin-76</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>41</td>
<td>40</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57 ± 10</td>
<td>60 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Severity of CAD</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(no. of patients with ≥75% obstruction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vessel disease</td>
<td>5</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>One vessel disease</td>
<td>7</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Two vessel disease</td>
<td>8</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Three vessel disease</td>
<td>21</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>Left main lesion</td>
<td>7</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(no. of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic stenosis/aortic regurgitation</td>
<td>1</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>59 ± 10</td>
<td>62 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume index (ml/m²)</td>
<td>80 ± 19</td>
<td>75 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>13 ± 6</td>
<td>12 ± 6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation. CAD = coronary artery disease; NS = no significant difference between the iopamidol and Renografin-76 groups.

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**Table 2. Medications Administered Immediately Before Angiography**

<table>
<thead>
<tr>
<th></th>
<th>Iopamidol</th>
<th>Renografin-76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting nitrates</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>Beta-adrenergic blocking agents</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Calcium channel blocking agents</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Digoxin</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Antiarrhythmic agents</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Diuretic drugs</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Antihypertensive agents</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Data represent number of patients.
was a significant difference in the prolongation of the QT interval produced by two contrast agents (p < 0.0001). At the end of the 60 second period, there was still a significant increase in the QT interval in the Renografin-76 group compared with the control value (p < 0.001), and a significant difference between the two contrast agent groups (p < 0.001). Selective injections of the right coronary artery produced a similar change in the QT interval; the difference between the two contrast agents was again highly significant (p < 0.0002).

There was no significant change in the RR interval in the iopamidol-treated patients after selective injections of either the right or left coronary artery. However, in the patients receiving Renografin-76 there was a significant increase in the RR interval from 0.98 ± 0.15 to 1.32 ± 0.46 seconds after left coronary angiography (p < 0.001) and a similar increase from 0.98 ± 0.15 to 1.26 ± 0.44 seconds after right coronary angiography (p < 0.001) (Fig. 3). The QRS duration was 0.08 ± 0.01 second in the Renografin-76 group.

**Table 3. Baseline Hemodynamic and Electrocardiographic Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Iopamidol</th>
<th>Renografin-76</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>141 ± 24</td>
<td>146 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>13 ± 6</td>
<td>12 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>QT interval (ms)</td>
<td>386 ± 31</td>
<td>386 ± 28</td>
<td>NS</td>
</tr>
<tr>
<td>RR interval (seconds)</td>
<td>1.00 ± 0.11</td>
<td>0.98 ± 0.14</td>
<td>NS</td>
</tr>
<tr>
<td>ST segment displacement (mm)</td>
<td>0.0 ± 0.3</td>
<td>0.0 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>T wave amplitude (mm)</td>
<td>1.6 ± 1.6</td>
<td>1.4 ± 1.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

All electrocardiographic variables were measured in lead II. One millivolt = 10 mm. NS = no significant difference between the iopamidol and Renografin-76 groups. Data are presented as mean ± 1 standard deviation.

Figure 1. The systolic arterial pressure (top) is shown for control (time 0) and for the 2 minute period after left ventriculography for the 41 iopamidol (▲—▲) and 40 Renografin-76 (●—●) patients. The left ventricular end-diastolic pressure (bottom) is also shown for the control period and after the left ventriculogram. The left ventriculogram was performed immediately after the control values (time 0). The data are presented as mean ± 1 standard error. ▲ p < 0.05 iopamidol versus Renografin-76; ■ p < 0.01 iopamidol versus Renografin-76; ■ p < 0.005 iopamidol versus Renografin-76; ♦ p < 0.001 iopamidol versus Renografin-76; ♦ p < 0.05 versus control; ♦ ♦ p < 0.01 versus control; ♦ ♦ ♦ p < 0.005 versus control; * * p < 0.001 versus control.

Figure 2. The systolic arterial pressures immediately before (time 0) and for the 2 minutes after the first selective contrast injection of the right coronary artery (top) and the left coronary artery (bottom) are plotted. The data are presented as mean ± 1 standard error. ▲—▲ represent the values in the iopamidol group and ●—● in the Renografin-76 group. Symbols for probability (p) values as in Figure 1.
76 group and 0.08 ± 0.02 second in the iopamidol group (p = NS). After selective coronary injection of the contrast agents, 19 of the 40 patients treated with Renografin-76 developed an intraventricular conduction defect with the duration of the QRS complex greater than 0.10 second, whereas only 3 of the 41 iopamidol-treated patients had prolongation of the QRS complex (p < 0.01).

Figure 3. The changes in the QT intervals, RR intervals, ST segments and T wave amplitudes induced by the contrast injections of the left coronary artery (left) and right coronary artery (middle) and by left ventriculography (right) are shown. The data are presented as mean ± 1 standard error. ▲—▲ represent the changes after iopamidol injection and •—• after Renografin-76 injection. Measurements and symbols for probability (p) values as in Figures 1 and 2.
With right coronary artery injections of Renografin-76, electrocardiographic analysis of lead II demonstrated significant ST segment depression from 0.0 ± 0.5 to −0.9 ± 1.1 mm (p < 0.001) and marked T wave inversion from an amplitude of 1.4 ± 1.2 to −2.2 ± 2.6 mm (p < 0.001) (Fig. 3). At the end of 60 seconds, there was still a significant decrease in T wave amplitude compared with the control value in the Renografin-76 group (p < 0.001). With iopamidol, there was ST segment depression from 0.0 ± 0.3 to −0.3 ± 0.6 mm at 5 seconds after the contrast injection (p < 0.005), but there was no significant change in T wave amplitude. A repeated measures analysis of variance showed that there was a significant difference in the ST segment and T wave amplitude response for the two contrast agents (p < 0.05 and p < 0.0001, respectively).

With the left coronary injections there was a significant elevation in the ST segment and a significant increase in T wave amplitude in lead II with Renografin-76. With iopamidol, there was no significant change in these two variables (Fig. 3).

Serious arrhythmias. Two of the patients in the Renografin-76 group developed ventricular fibrillation during selective injection of the right coronary artery; the arrhythmia was immediately treated with electrical cardioversion and there were no late sequelae in either patient. There were no episodes of ventricular tachycardia or fibrillation in the iopamidol group.

There was a significant but brief decrease in the heart rate immediately after injections of both the right and left coronary arteries with Renografin-76 (Fig. 3), whereas with iopamidol there was no significant change in the heart rate. All patients in this study had a temporary pacing catheter placed in the right ventricle which was used for periods of asystole lasting 2.5 seconds or more. Eight of the 40 patients receiving Renografin-76 required pacing during the coronary injections. However, none of the 41 patients in the iopamidol group was paced during the procedure. This difference in the development of serious bradyarrhythmias during coronary injections is significant (p < 0.01).

Chest pain. It is not uncommon for patients to experience transient chest pain and feelings of warmth during and immediately after selective contrast injections of the coronary arteries and during left ventriculography. After the procedure, each patient was asked to grade these subjective feelings of pain and warmth that occurred during angiography. Thirty-three of the 40 patients receiving Renografin-76 had no chest pain during the intravascular bolus injection for the left ventriculogram. Likewise, 37 of the 41 patients in the iopamidol group had no pain. There was no significant difference between the two groups for chest pain induced by the left ventriculogram. However, on a scale of 0 to 10 for the sensation of warmth associated with the left ventriculogram, the mean score was 7.0 ± 2.5 for the Renografin-76 group and 4.2 ± 2.3 for the iopamidol group; this difference was significant (p < 0.05).

During selective coronary angiography, 25 of the 40 patients treated with Renografin-76 had chest pain, whereas only 11 of the 41 iopamidol-treated patients had pain (p < 0.005). In the Renografin-76 group, the mean score for pain during the selective coronary angiography was 3.1 ± 3.0 and the score for warmth was 2.8 ± 2.7. In comparison, the mean scores for the iopamidol group were 0.8 ± 1.6 and 1.1 ± 2.0, respectively. The differences for both pain and warmth during coronary angiography were significant (p < 0.05). In most patients, the chest pain associated with the contrast injection was very transient and required no treatment. However, 13 of the patients treated with Renografin-76 required nitroglycerin for their chest pain associated with coronary angiography. Only five of the iopamidol-treated patients had chest pain requiring treatment with nitroglycerin during the study.

Other side effects. Two of the patients receiving Renografin-76 developed nausea and vomiting after contrast injection. None of the patients in the iopamidol group had gastrointestinal symptoms during or after the procedure.

There was no difference in the mean creatinine clearance between the two groups; the mean value for the calculated creatinine clearance was 81 ± 23 ml/min in the patients treated with Renografin-76 and 85 ± 25 ml/min in the iopamidol-treated patients. Two patients receiving Renografin-76 had deterioration of their renal function after angiography, as defined by a 0.5 mg/dl increase in serum creatinine. In these patients, the creatinine increased from 1.3 and 1.2 mg/dl (control) to 2.3 and 2.6 mg/dl, respectively, 48 hours after angiography. In the iopamidol group, only one patient had a similar increase in serum creatinine from 1.2 to 1.7 mg/dl. In all three patients, the deterioration in renal function was transient.

Quality of cineangiograms. Both contrast agents contain 370 mg iodine/ml and produced very good to excellent visualization of the coronary anatomy. We could not detect a difference in the cineangiographic quality of the left ventriculograms and the selective coronary angiograms between iopamidol and Renografin-76.

Discussion

Safety of cardiac angiography. Morbidity and mortality associated with selective coronary angiography and left ventriculography have decreased in the last decade (43–45). Many of the remaining complications are directly related to the contrast medium. There is a decrease in systemic arterial pressure and an increase in left ventricular end-diastolic pressure immediately after an intravascular bolus injection of an ionic contrast medium for the left ventriculogram (5.7–9.13,31,34,35). Selective coronary injections of these ionic agents are associated with bradyarrhythmias, prolongation of the QRS complex, increase in the QT interval, marked shifts in the ST segment and T wave changes (1–3,10,29,31,34,46). Development of contrast agents that
are less toxic to the myocardium than these standard ionic agents should enhance the safety of angiographic procedures.

Animal studies (15,28-31,38) have shown that the new nonionic agents are associated with fewer hemodynamic and electrocardiographic changes compared with ionic contrast media. Measurements of myocardial contractility have shown that these new agents have a small positive inotropic effect as opposed to the negative inotropic effects of the ionic agents (15,20,33,35). These nonionic agents have been evaluated in several human studies (32,34,39,40), and their results corroborate the findings of the animal studies, suggesting that these new agents are safer.

This is the first large study that compares iopamidol and Renografin-76 in human subjects in a double-blind randomized fashion. Our data demonstrate that the hemodynamic and electrocardiographic changes induced by contrast left ventriculography and coronary angiography were significantly less when the nonionic agent, iopamidol, was compared with a standard ionic contrast medium. The incidence and severity of bradyarrhythmias and systemic hypotension were greater with Renografin-76 compared with iopamidol. Prolongation of the QT interval, widening of the QRS complex and ST and T wave changes were also significantly greater in the Renografin-76 group compared with the iopamidol group. These findings indicate that iopamidol is less toxic to the myocardium compared with Renografin-76.

Ventricular fibrillation. Ventricular fibrillation is one of the most serious complications associated with coronary angiography and is directly associated with injections of contrast agent. Although there is no direct relation between development of ventricular fibrillation and changes in the QT interval, prolongation of the QT interval is considered a risk factor for ventricular arrhythmia (46-49). In this study, the increase in the QT interval was significantly greater with Renografin-76 than with iopamidol (p < 0.0002). If there were a direct relation between prolongation of QT interval and ventricular fibrillation, one might expect a higher incidence of ventricular fibrillation in the Renografin-76 group. In our study, 2 of the 40 patients in the Renografin-76 group developed ventricular fibrillation during selective coronary angiography, whereas none of the 41 patients receiving iopamidol had this complication. Although the number of patients in this study is too small to determine the true incidence of ventricular fibrillation for each contrast agent, our data suggest that the incidence of ventricular fibrillation may be higher for Renografin-76 than for iopamidol. Using Renografin-76 as the contrast agent, the incidence in our laboratory of ventricular tachycardia-fibrillation is 1.5%. This was determined in 260 consecutive cases performed after the completion of this double-blind study.

Heterogeneity of depolarization and repolarization within adjacent areas of the myocardium is one of the proposed mechanisms of contrast-induced ventricular fibrillation. Franz et al. (50) measured indexes of depolarization and repolarization during the coronary injections of iopamidol and Renografin-76 in dogs. They found that Renografin-76 caused a significantly greater prolongation of the monophasic action potential compared with iopamidol. Their findings also suggest that the risks of ventricular arrhythmias are higher with Renografin-76 than with iopamidol.

Biochemical data. We (17) and Visioli et al. (18) have demonstrated that contrast ventriculography with Renografin-76 induces changes in myocardial metabolism. Recently (51), we have investigated the myocardial metabolic effects of iopamidol and have shown that the decrease in myocardial lactate extraction that occurs after injection of Renografin-76 did not occur with this new nonionic agent. Using [1-14C]lactate as a tracer, we measured the amount of lactate released by the myocardium before and after an injection of Renografin-76 and iopamidol. After injection of Renografin-76, there was a 54 ± 38% increase in myocardial lactate release, whereas after iopamidol there was no significant change in the amount of lactate released (52). These biochemical data suggest that contrast angiography with the standard ionic agents induces myocardial cellular ischemia and that the newer nonionic agent, iopamidol, does not produce these changes.

Factors influencing contrast medium toxicity. In addition to the contrast ion or molecule, there are a number of other important differences between these two contrast agents, such as osmolality and cation composition and content. The contribution of these factors to the electrocardiographic and hemodynamic differences observed in this study is unclear. Many reports (5,7,12,13,15,19,20,28,35,53) have indicated that the toxicity of a contrast agent is directly related to the osmolality. The osmolality of Renografin-76 (1,680 mosm/kg) is approximately twice that of iopamidol (796 mosm/kg) (34,36,38). Recently, an ionic contrast agent (ioxaglate) has been developed which has an osmolality similar to iopamidol (20,31,38,53). Tragardh and Lynch (31) compared the effects of ioxaglate, diatrizoate (Renografin-76) and two nonionic compounds during coronary angiography in animals. Their study demonstrated that both nonionic agents were associated with fewer hemodynamic and electrophysiologic changes than the new ionic low osmolality contrast agent. Although osmolality plays an important role in contrast agent toxicity, the study by Tragardh and Lynch (31) suggests that it is not the only factor. The cation composition and content of the contrast agent also appear to be important factors (15,19,20,22,23,46,54-56). Iopamidol has negligible amounts of sodium compared with 190 mEq/liter in Renografin-76. Renografin-76 has no calcium and iopamidol contains only negligible amounts of calcium. Contrast agents with varying sodium and calcium contents have been evaluated (15,20,22,23,56). Although the addition of calcium appears to decrease the toxicity, the
entire cardiodepressant effect of the contrast medium is not eliminated. Further studies are needed to elucidate the mechanisms for the differences in the toxicity we observed between iopamidol and Renografin-76.

**Clinical implications.** This study has shown that the incidence of malignant bradyarrhythmias and the severity and duration of hypotension after left ventriculography and coronary angiography is significantly less with iopamidol than with the standard ionic agent, Renografin-76. The incidence of ventricular fibrillation may also be less with iopamidol compared with Renografin-76. Other electrocardiographic and hemodynamic variables measured in this study indicate that iopamidol is less toxic to the myocardium. Therefore, this nonionic agent appears to increase the safety of cardiac angiography. In addition, the discomfort experienced by the patient was considerably less with iopamidol compared with the ionic agent. The cineangiographic quality of the two contrast agents was similar. Increasing the safety of cardiac angiography without compromising excellent cineangiographic results makes this new nonionic contrast agent, iopamidol, superior to the standard ionic agents.

The cost of this new nonionic contrast medium will probably be greater than the standard ionic contrast agents. Further studies are needed to address the cost/benefit ratio of these new agents. Although the costs may preclude their use in all patients undergoing angiography, we believe that patients at high risk, such as those with impending myocardial infarction, unstable angina, impaired ventricular function, or recurrent ventricular arrhythmias, will benefit greatly through the use of these nonionic agents in cardiac angiography.

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