Identification and Description of Separate Mechanisms for Two Components of Renografin Cardiotoxicity

KENNETH A. POPIO, M.D., ANDREW M. ROSS, M.D., JOHN M. ORAVEC, B.A., AND JAMES T. INGRAM, B.A.

SUMMARY Both hemodynamic and electrocardiographic effects of Renografin-76 (diatrizoate meglumine) were studied in intact, anesthetized dogs. The left coronary artery in nine dogs was injected with equal amounts of Renografin-76, an equiosmolar dextrose solution (1690 mOsm/l) and a solution of the same electrolytic content (190 mEq/l sodium). Renografin and the dextrose solution produced significant sinus slowing, axis shift and prolongation of PR, QRS and QT intervals. On the other hand, Renografin and the electrolytic solution caused arterial hypotension, elevation of the left ventricular end-diastolic pressure and depression of left ventricular dP/dt. The dextrose solution did not impair left ventricular hemodynamic performance while the only electrocardiographic effect of the electrolytic solution was QT lengthening. None of the effects of any solution were modified by atrial pacing, and thus were independent of bradycardia.

Four other dogs underwent left coronary arterial injections of 1) Renografin-76, 2) Renografin-76 with 40 mEq/l Ca++, 3) the previously used electrolytic solution, 4) the electrolytic solution with 40 mEq/l Ca++, and 5) a saline solution with 190 mEq/l Na+. The addition of Ca++ ameliorated but did not prevent the hemodynamic effects of the electrolytic solution. When added to Renografin, however, slight elevation of systemic blood pressure and marked increase in dP/dt were seen.

We conclude that hyperosmolarity is responsible for the deleterious electrocardiographic effects of Renografin, while hypocalcemia induced by calcium-chelating agents is at least partly responsible for hemodynamic depression. The creation of a new contrast agent with more physiologic osmolarity and electrolytic composition would be preferable to attempts at altering currently available media.

THE INJECTION of angiographic contrast media into the coronary arteries causes transient electrophysiologic and hemodynamic changes.1-4 These include bradycardia, widening of the PR and QRS intervals, repolarization abnormalities, shift in the electrical axis, hypotension and depression of generated myocardial force. Many recent investigations have attempted to delineate the etiology and mechanisms of the deleterious electrocardiographic effects. Some studies have tried to isolate the various constituents of contrast media responsible for these changes. Both animal and human data suggest the electrocardiographic T wave changes are secondary to injected sodium concentration5,6 and that sinus slowing is a function of hyperosmolarity.1,4,8 The genesis of the known hemodynamic effects has been less systematically examined. Some investigators have suggested that hyperosmolarity was responsible for these changes too. However, the calcium-chelating agents in many contrast media have more recently been implicated as a factor.12-15

In this study, we have extended investigations into the mechanisms of all of the cardiac effects of the most commonly used coronary angiographic contrast agent, Renografin (dinitrosoate meglumine). Both hemodynamic and electrocardiographic effects of coronary arterial injections of this contrast medium were compared with the effects of solutions designed to mimic and isolate certain characteristics. Solutions were formulated to have the same osmolarity but with no sodium content or the same sodium content but less osmolarity. The second part of the experiment studied the effect of added calcium upon Renografin's adverse cardiac responses.

Methods

Effects of Hyperosmolarity Contrasted with Effects of the Electrolytic Component

In the first part of the experiment, eight mongrel dogs weighing between 20–30 kg were anesthetized using chloralose (500 mg/kg i.V.) for the first three dogs and sodium pentobarbital (30 mg/kg i.V.) for the other five dogs. Continuous ventilation was provided with room air via a cuffed endotracheal tube connected to a positive pressure breathing apparatus. Each animal was anticoagulated with 5,000 units of I.V. heparin sulphate. The right femoral artery was catheterized using a modified Judkins 7F left coronary artery catheter, which was advanced to the orifice of the left coronary artery (LCA) whenever injections were made. The right jugular vein was catheterized with a 7F bipolar pacing electrode which was positioned in the right atrium for the purpose of atrial overdrive pacing. Direct left ventricular pressure was obtained with a Millar transducer-tipped catheter inserted into the right carotid artery with its tip positioned in the left ventricle. Electronic manipulation of the resultant high-fidelity signal allowed simultaneous left ventricular end-diastolic pressure...
(LVEDP) and the first derivative of the left ventricular pressure (dP/dt) to be measured. Both maximal positive and negative dP/dt were noted. Aortic pressure was measured with a Statham P23 db transducer attached to a #18 Longdwell catheter inserted into the left carotid artery.

Pressure data were registered simultaneously with electrocardiographic limb lead II on a Clevite-Brush Mark 260 6-Channel direct writing recorder. In addition, six standard limb electrocardiographic leads were simultaneously recorded on a Mingograph model 81 electrocardiograph machine at 100 mm/sec paper speed. Electrocardiographic measurement included R-R, PR, QRS and QT intervals. The height of the R wave was measured in standard lead II assuming that a change would reflect a change in electrical axis. Changes in R wave height did correlate with mean QRS axis shift in the five dogs in which this was evaluated. All variables were recorded before each injection (baseline) and continuously during the 60 seconds following the left coronary injection of each test solution; measurements were made every 5 seconds throughout the recording period. Solutions were 1) 5 ml of Renografin-76 (190 mEq/l total sodium content, including 0.32% sodium citrate and 0.04% disodium edetate; total osmolarity 1690 mOsm/l); 2) 5 ml of a sterile electrolyte solution containing 190 mEq/l sodium including sodium bicarbonate and chloride, 0.32% sodium citrate, and 0.04% disodium edetate, buffered to provide a pH between 7.0 and 7.5, and having 395 mOsm/l; and 3) 5 ml of a sterile glucose solution with an osmolarity of 1690 mOsm/l and pH between 7.0 and 7.5. Each injection was made manually into the left coronary artery via the modified Judkins catheter over approximately 3 or 4 seconds. Before each injection, small amounts (less than 1 ml) of Renografin were injected to ascertain that subsequent injections would be into the coronary lumen. Three minutes were allowed for dissipation of any effects secondary to such small contrast medium injections before subsequent injections of test solutions.

All three solutions were injected in a control state with the intact animal anesthetized and instrumented. Similar injections were then repeated while pacing the right atrium at a rate 10% above the animal's baseline heart rate to exclude any effects due to solution-induced bradycardia. The order of injection of the solutions was varied randomly during each state (i.e., control and pacing) for each animal. All animals were sacrificed at completion of the study.

Effects of Added Calcium

In the second part of the experiment, four dogs were prepared and anesthetized with chloralose as described earlier. The solutions injected, however, were different, and injections were not made during atrial pacing. The solutions used here included 1) Renografin-76 with 40 mEq/l calcium chloride added, 2) Renografin-76 as used in the first part of the experiment, 3) the electrolyte solution as used in the first part of the experiment, 4) the electrolyte solution with 40 mEq/l calcium chloride, and 5) a saline solution containing 190 mEq/l sodium. As before, 5 ml quantities of each solution were injected in random order. A total of six complete series of injections was performed in the four animals.

Statistical Analysis

Comparison between baseline observations and subsequent measurements for each parameter was made using paired Student t test. Analyses of variance and covariance were employed to test the overall regression of observations on the control readings, as well as the interaction of atrial pacing with time of observations (shape of response curve). Likewise, the effects of added calcium were measured by the same statistical methods.

Results

Tables 1 and 2 show both baseline values and the peak change measurements of R-R, PR, QRS and QT

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**Table 1. Degree of Changes Occurring After Injections in the Control State**

<table>
<thead>
<tr>
<th></th>
<th>R-R (msec)</th>
<th>PR (msec)</th>
<th>QRS (msec)</th>
<th>QT (msec)</th>
<th>R Wave height (mm)</th>
<th>Aortic pressure (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>Max dP/dt (mm Hg/sec)</th>
<th>Max negative dP/dt (mm Hg/sec)</th>
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</thead>
<tbody>
<tr>
<td><strong>Renografin</strong></td>
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<tr>
<td>B</td>
<td>505 ± 21</td>
<td>106 ± 3</td>
<td>54 ± 4</td>
<td>245 ± 7</td>
<td>16.5 ± 2</td>
<td>130 ± 6</td>
<td>99 ± 5</td>
<td>4 ± 1</td>
<td>1072 ± 170</td>
</tr>
<tr>
<td>P</td>
<td>529 ± 25†</td>
<td>114 ± 3†</td>
<td>59 ± 5*</td>
<td>327 ± 11†</td>
<td>22.7 ± 2†</td>
<td>94 ± 6‡</td>
<td>70 ± 5‡</td>
<td>7 ± 1†</td>
<td>598 ± 65†</td>
</tr>
<tr>
<td><strong>Dextrose</strong></td>
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<tr>
<td>B</td>
<td>519 ± 18</td>
<td>108 ± 3</td>
<td>53 ± 3</td>
<td>247 ± 9</td>
<td>14.8 ± 2</td>
<td>131 ± 8</td>
<td>95 ± 4</td>
<td>3 ± 1</td>
<td>1081 ± 155</td>
</tr>
<tr>
<td>P</td>
<td>534 ± 20*</td>
<td>109 ± 3</td>
<td>56 ± 4*</td>
<td>276 ± 9‡</td>
<td>17.6 ± 2†</td>
<td>136 ± 7†</td>
<td>97 ± 4</td>
<td>4 ± 1</td>
<td>1356 ± 175‡</td>
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<tr>
<td><strong>Electrolyte</strong></td>
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<tr>
<td>B</td>
<td>506 ± 21</td>
<td>106 ± 2</td>
<td>53 ± 4</td>
<td>243 ± 8</td>
<td>14.9 ± 2</td>
<td>135 ± 8</td>
<td>100 ± 5</td>
<td>4 ± 1</td>
<td>1132 ± 165</td>
</tr>
<tr>
<td>P</td>
<td>507 ± 21</td>
<td>106 ± 2</td>
<td>53 ± 4</td>
<td>297 ± 11‡</td>
<td>15.4 ± 2</td>
<td>110 ± 5‡</td>
<td>79 ± 5‡</td>
<td>7 ± 1‡</td>
<td>648 ± 71‡</td>
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*P < 0.05.
†P < 0.01.
‡P < 0.001.
Abbreviations: B = baseline; LVEDP = left ventricular end-diastolic pressure; Max = maximal; P = peak; diast = diastolic; syst = systolic.
TABLE 2. Degree of Changes Occurring After Injections During Atrial Pacing

<table>
<thead>
<tr>
<th></th>
<th>R-R (msec)</th>
<th>PR (msec)</th>
<th>QRS (msec)</th>
<th>QT (msec)</th>
<th>R Wave height (mm)</th>
<th>Aortic pressure (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>Max dP/dt (mm Hg/sec)</th>
<th>Max negative dP/dt (mm Hg/sec)</th>
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<tr>
<td>Renografin</td>
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<td></td>
<td></td>
<td>syst</td>
<td>diast</td>
<td></td>
<td></td>
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<tr>
<td>B</td>
<td>419 ± 66</td>
<td>117 ± 5</td>
<td>54 ± 4</td>
<td>237 ± 10</td>
<td>14.8 ± 2</td>
<td>131 ± 8</td>
<td>102 ± 8</td>
<td>2 ± 1</td>
<td>1228 ± 184</td>
</tr>
<tr>
<td>P</td>
<td>419 ± 66</td>
<td>125 ± 61*</td>
<td>59 ± 6*</td>
<td>271 ± 33†</td>
<td>20.9 ± 2†</td>
<td>101 ± 7†</td>
<td>79 ± 6†</td>
<td>5 ± 1†</td>
<td>812 ± 106†</td>
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<td></td>
<td></td>
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<tr>
<td>B</td>
<td>415 ± 21</td>
<td>119 ± 5</td>
<td>56 ± 4</td>
<td>222 ± 14</td>
<td>14.2 ± 3</td>
<td>133 ± 9</td>
<td>99 ± 6</td>
<td>2 ± 1</td>
<td>1269 ± 214</td>
</tr>
<tr>
<td>P</td>
<td>415 ± 21</td>
<td>123 ± 4*</td>
<td>59 ± 4</td>
<td>246 ± 17†</td>
<td>16.6 ± 2*</td>
<td>137 ± 8</td>
<td>101 ± 5</td>
<td>2 ± 1</td>
<td>1519 ± 210†</td>
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<tr>
<td>Electrolyte</td>
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<td></td>
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<tr>
<td>B</td>
<td>414 ± 21</td>
<td>118 ± 6</td>
<td>55 ± 3</td>
<td>229 ± 14</td>
<td>13.7 ± 2</td>
<td>135 ± 8</td>
<td>100 ± 6</td>
<td>2 ± 1</td>
<td>1219 ± 193</td>
</tr>
<tr>
<td>P</td>
<td>414 ± 21</td>
<td>118 ± 6</td>
<td>55 ± 3</td>
<td>266 ± 16†</td>
<td>14.1 ± 2</td>
<td>112 ± 6†</td>
<td>83 ± 7†</td>
<td>5 ± 5*</td>
<td>800 ± 95†</td>
</tr>
</tbody>
</table>

*P < 0.05.  †P < 0.001.
Abbreviations: B = baseline; LVEDP = left ventricular end-diastolic pressure; Max = maximal; P = peak; diast = diastolic; syst = systolic.

Intervals, R wave height, aortic systolic and diastolic pressures, LVEDP, maximal positive dP/dt and maximal negative dP/dt after injection of Renografin, electrolyte and dextrose solutions. All maximal deviations from baseline values occurred 10–15 seconds after injections. All values represent the arithmetic mean of observations for all eight dogs. Standard errors (SEM) are also shown. Peak change measurements that are statistically different from their respective baseline observations are noted. Table 1 reports the effects seen in the control state, and table 2 shows those occurring with pacing.

Electrophysiologic Variables

Figure 1 and table 1 display the effects of the three solutions used in the first part of this experiment upon all electrocardiographic measurements made in the control state. Renografin injection produced significant sinus bradycardia, the R-R interval increasing from 505 ± 21 msec to 528 ± 25 msec (P < 0.01). The slowing was maximal 15 seconds after injection and was essentially resolved by 40 seconds Dextrose simulated this change, but was less marked (baseline 518 ± 18 msec rising to 534 ± 20 msec) (P < 0.05).

The electrolyte solution, on the other hand, produced no change in the R-R interval. Renografin also increased the QRS from 54 ± 4 msec to 59 ± 5 msec (P < 0.05) and dextrose increased it from 53 ± 3 msec to 56 ± 4 msec (P < 0.05), while the electrolyte solution produced no change. Renografin caused an increase in R wave amplitude from 16.5 ± 2 mm to 22.7 ± 2 mm (P < 0.001) while dextrose produced a change from 14.8 ± 2 mm to 17.6 ± 2 mm (P < 0.01) and the electrolyte solution again had no effect. Only Renografin, however, caused prolongation of the PR interval in the control state (106 ± 3 msec to 114 ± 3

**Figure 1.** Time course of changes in electrocardiographic variables after injections of Renografin-76, dextrose solution, and electrolyte solution (sodium). All points are the arithmetic mean values for eight dogs.
msec, $P < 0.01$). All three solutions produced significant lengthening of QT intervals: Renografin from $245 \pm 7$ msec to $327 \pm 11$ msec ($P < 0.001$); dextrose from $247 \pm 9$ msec to $276 \pm 9$ msec ($P < 0.001$); and electrolyte from $243 \pm 8$ msec to $297 \pm 11$ msec ($P < 0.001$). Table 2 shows that although atrial pacing was successful in preventing sinus bradycardia, essentially all other changes were unaffected. In fact, dextrose injections were now accompanied by significant shortening of the PR interval ($119 \pm 5$ msec to $123 \pm 4$ msec, $P < 0.05$).

Hemodynamic Variables

The hemodynamic measurements made during the control state are shown in figure 2 and table 1. Renografin caused a marked decrease in both systolic and diastolic aortic pressures. The mean systolic pressure fell from $130 \pm 5$ mm Hg to $94 \pm 6$ mm Hg ($P < 0.001$), and the diastolic from $99 \pm 5$ mm Hg to $70 \pm 5$ mm Hg ($P < 0.001$). Similar changes were seen after the injection of the electrolyte solution. Mean systolic pressures fell from $135 \pm 8$ mm Hg to $110 \pm 5$ mm Hg ($P < 0.001$), while the mean diastolic pressures decreased from $100 \pm 5$ mm Hg to $79 \pm 5$ mm Hg ($P < 0.001$). Dextrose injections, on the other hand, were associated with slight increases in both these pressures. Mean systolic pressures rose from $131 \pm 8$ mm Hg to $136 \pm 7$ mm Hg ($P < 0.01$), and diastolic from $95 \pm 4$ mm Hg to $97 \pm 4$ mm Hg. Highly significant decreases in both maximal positive and negative $dP/dt$ were seen following both Renografin and electrolyte solution injections, while dextrose injections were associated with an increase in the positive $dP/dt$ and insignificant change in the negative value. Values for these parameters are listed in table 1. Mean LVEDP rose from $4 \pm 1$ mm Hg to $7 \pm 1$ mm Hg ($P < 0.01$) after either Renografin or electrolyte solution injections. There was essentially no change in this measurement after the injection of equiosmolar dextrose. Table 2 shows that all of these changes continued to occur despite atrial pacing.

Effect of Added Calcium

Table 3 shows baseline values and peak change measurements of all hemodynamic parameters measured in the second part of this experiment. The values are the arithmetic mean ± SEM for six series of injection in four dogs. Peak change measurements which are statistically different from their respective baseline measurements are shown. Figure 3 shows the time course of the responses of the hemodynamic variables to injections of Renografin-76 and Renografin with added calcium. The addition of 40 mEq/l Ca++ eliminated Renografin's changes upon aortic diastolic pressure and LVEDP. However, instead of the hypotension seen with unaltered Renografin-76, there was a slight rise in blood pressure. Likewise, instead of the fall in positive maximal $dP/dt$, there was a rather marked rise. The latter rise began with 5 seconds and peaked at 15 seconds, in contrast to the time course seen with Renografin alone, where the nadir occurred at 5 seconds and the "rebound" peak at 20 seconds. The addition of 40 mEq/l Ca++ to the electrolyte solution used in the first part of this study produced a different result from that just described for Renografin. This addition attenuated all of the detrimental hemodynamic effects seen with its parent solution. None of the effects were prevented, however. Finally, the saline solution produced no significant alteration in any variable, although the direction of change in each instance was similar to that seen after both parent solutions of Renografin and its electrolyte component.

Figures 4 and 5 are a comparison of the degrees of

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**Figure 2.** Time course of changes in hemodynamic variables after injections of Renografin-76, dextrose solution, and electrolyte solution (sodium). Values plotted are the arithmetic mean of observations on eight dogs.
change produced by each parent solution and its counterpart with added calcium. The changes produced by the two modified solutions and the changes secondary to saline injections are shown. Only greatest changes are shown. The addition of calcium to both Renografin and electrolyte solutions made significant alterations in the systemic systolic arterial pressure response to the injection of their respective parent compounds. However, the response provoked by the calcium-modified electrolyte solution is significantly different (P < 0.05) from that produced by Renografin with calcium added. A similar pattern was seen with maximal positive dP/dt, except that the difference between the responses secondary to the two calcium-added solutions was more striking (P < 0.01). The addition of calcium to Renografin and electrolyte solutions attenuated the decrease in aortic diastolic pressures and increase in LVEDP seen with the parent compound. In these two instances, there was no difference between the effect of Renografin with calcium and similarly modified electrolyte components.

**Discussion**

The incidence of adverse side effects associated with coronary angiography has decreased. Nevertheless, adverse effects still occasionally occur. These side effects are probably the result of several factors: the severity of obstructive coronary lesions, the magnitude of its effect upon the myocardium, and the radiographic contrast agent used in the procedure. Thus, the only practical, possible way to further decrease morbidity and mortality secondary to this diagnostic investigation is through improvement of the contrast agent.

The adverse effects of Renografin-76 on cardiac physiology are well-known, and include both electrophysiologic and hemodynamic depression. The latter includes hypotension and depression of generated myocardial force. Among the observed adverse electrophysiologic effects are sinus bradycardia, prolongation of A-H conduction, shifts in electrical axis and ST-T wave changes. The most dangerous of these effects are the hemodynamic changes and sinus slowing, which might lead to further compromises in coronary perfusion in patients whose myocardial oxygen supply is already limited by their disease.

Despite intensive investigation, there remains considerable controversy as to the basis for the electrophysiologic effects. Early studies by Paulin et al. indicated that the incidence of ventricular fibrillation was increased if the sodium concentration in the injected was either too high or too low. Subsequent angiographic media with sodium concentrations similar to plasma levels have greatly reduced the occurrence of this dangerous arrhythmia. However, bradycardia and conduction abnormalities have continued to occur with the same frequency. Many studies have examined the effects of the hyperosmolarity of current media by measuring electrocardiographic changes pursuant to the injection of solutions of varying osmolarities into coronary arteries. The uniform conclusion has been that the degree of sinus node depression has been directly related to the hyperosmolarity of the injected solution. Consequently, efforts are currently under way to develop contrast media of lesser os-
molarity. Metrizamide, a non-ionic agent, is currently being tested in Europe.\(^9, 13, 21, 22\) Recently, however, controversy arose when a cellular electrophysiologic investigation\(^23\) showed that the “slow response” produced by Renografin in Purkinje tissue is not simulated by another hyperosmolar solution, mannitol.

The hemodynamic depression produced by contrast agents has not been studied so intensively. Most attention has focused upon the presence of calcium-chelating agents within Renografin and the decrease in calcium content that has been observed in coronary venous blood after arteriography.\(^14\) Tragardh\(^13\) has found that the addition of calcium to Renografin ameliorated the hemodynamic depression usually seen. However, other investigators have attributed hemodynamic depression to the effects of hyperosmolarity. Wolf\(^11\) noted the same degree of depression of contractility with both Renografin-76 and 5% sodium chloride injected in isolated perfused dog heart. Since both solutions were hyperosmolar, he concluded that this characteristic was responsible. Although there is still confusion as to the feature of the contrast agent that is responsible for hemodynamic depression, it is generally agreed that the effect is direct, since it can occur in such an isolated heart preparation.

The intent of this study was to investigate more systematically the basis for hemodynamic deterioration and to compare and contrast the effects of two of the major characteristics of Renografin, its osmolarity and its electrolyte content, within the same experimental model. Finally, in a second part of the study, the importance of calcium-chelation secondary to Renografin was examined.

The LCA was chosen for injections to facilitate the demonstration of locally produced hemodynamic changes since almost all of the left ventricle is supplied

**Figure 3.** Comparison of time course of changes in hemodynamic variables after injections of Renografin-76 and Renografin-76 with 40 mEq/l added calcium. All points are the arithmetic mean values for six injections in four dogs.
by the LCA in the dog. In order to mimic the clinical circumstances as closely as possible, injections were made via preformed catheters introduced into the femoral artery of intact, anesthetized animals. In the first part of the study, two solutions were formulated; each of which mimicked only one isolated feature of the contrast agent. There was a dextrose solution of the same osmolarity (1690 mOsm/l) and an electrolyte solution of the same sodium content (190 mEq/l). The hemodynamic and electrophysiologic changes after injection of these solutions were then compared to alterations that occurred after Renografin was injected. The hyperosmotic dextrose solution and Renografin both produced sinus slowing, axis shifts, and prolongation of the QRS and QT intervals. Renografin always prolonged the PR interval, while dextrose only prolonged it significantly during atrial pacing. In general, the effects of Renografin were uniformly more striking than those of dextrose. However, the hyperosmotic solution did not produce
any of the hemodynamic changes seen after Renografin. On the other hand, the hypotension, decreased dP/dt (both positive and negative) and elevated LVEDP were all closely duplicated by the electrolyte solution. The only electrocardiographic change caused by the electrolyte solution was QT prolongation. Thus, while hyperosmolarity is largely responsible for electrophysiologic changes, only the electrolyte solution seems to reproduce the hemodynamic deterioration seen after use of Renografin. Similar injections done during atrial pacing demonstrated that none of these changes were simply secondary to the sinus bradycardia that was produced. Since the equiosmolar dextrose solution did not exactly duplicate the electrocardiographic depression seen after Renografin, some unknown additive factor must be present in Renografin.

In the second part of this experiment, we attempted to identify the specific aspect of the electrolyte solution that was responsible for the hemodynamic depression. Forty mEq/l of calcium was added to both Renografin and the electrolyte solution. The amount of calcium was chosen for two reasons: first, Caulfield et al. found in vitro that this amount would titrate the calcium-chelating effect of Renografin, and second, Tragardh suggested this as an optimal compromise from work performed in canines. Tragardh projected that higher doses of calcium (58–86 mEq/l) would eliminate arterial hypotension but found that when 50 mEq/l was added, LV dP/dt rose above preinjection values. Calcium did influence the cardiac depression, suggesting that these effects are secondary to the chelating agents in Renografin and not to its somewhat increased sodium content. However, the addition of the calcium produced some unexpected results. Whereas when added to the electrolyte solution it attenuated the deleterious effects as Tragardh predicted, 40 mEq/l of calcium added to Renografin produced a slight rise in arterial pressure and remarkable increases in dP/dt. While the elevated dP/dt was undoubtedly partially due to the rise in arterial pressure, the change in dP/dt occurred before and out of proportion to it. Furthermore, there was, in fact, only a rise in systolic pressure; diastolic arterial pressure did not change. Presumably, an increase in contractility also occurred, since heart rate fell slightly, and LVEDP was unchanged. The reason for this difference in response to the two solutions with added calcium is unclear. One cannot ascribe the increases to pharmacologic effects of added calcium, since they did not occur with the altered electrolyte solution. The effects cannot be secondary to differing sodium concentrations, since they are identical. Furthermore, hyperosmolarity did not produce any hemodynamic effects in the first part of this study, so it is unlikely to account for the difference.

The only remaining differences between the two modified solutions are the iodine content and the diatrizoate compounds. There is no evidence concerning cardiac effects of either of these. Nevertheless, regardless of its genesis, the rise in left ventricular dP/dt could increase myocardial oxygen need, which could be detrimental in patients being studied for coronary artery disease. Contrary to recent suggestions, the simple addition of 40mEq/l of calcium to the currently available arteriographic agent, Renografin, will not completely prevent cardiac depression. Electrophysiologic changes will continue unabated, and while hemodynamic depression may be relieved, an opposite, but perhaps equally dangerous effect, may be achieved. Smaller amounts of calcium, or the elimination of the calcium-chelating agents, might provide a better compromise, but electrophysiologic changes would still be unaffected. Increased efforts should be made to formulate new contrast media of both more physiologic osmolarity and electrolytic composition.

Acknowledgment

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References

Echocardiography of Left Ventricular Masses

THOMAS A. PORTS, M.D., JOHN COGAN, M.D., NELSON B. SCHILLER, M.D., AND ELLIOT RAPAPORT, M.D.

SUMMARY The M-mode and two-dimensional real-time echocardiographic findings in 10 patients with left ventricular masses are discussed. Two patients had left ventricular tumors and eight had left ventricular thrombi. In all cases the diagnosis was confirmed by angiography or surgery. The intracavitary and intramural left ventricular tumors were detected both by M-mode and two-dimensional echocardiography. M-mode echocardiography, however, did not detect the left ventricular thrombus in all instances. Two-dimensional echocardiography was able to identify the four large and inhomogeneous left ventricular thrombi but did not clearly identify four cases of smaller mural thrombi. Echocardiographic techniques useful in detection of left ventricular masses are discussed.

ALTHOUGH THE ROLE OF M-MODE echocardiography in the detection of many cardiac tumors is well-established,1-4 experience with tumors of the left ventricle is extremely limited.5-7 The reliability of echocardiography for the detection of left ventricular thrombi has not been assessed. In this paper we present the M-mode and two-dimensional echocardiographic findings of 10 patients with left ventricular masses. The reliability of echocardiography in the diagnosis of left ventricular masses is assessed, and techniques useful in the diagnosis of such lesions and potential sources of interpretive error are discussed.

Materials and Methods

We reviewed the preoperative echocardiographic findings of 15 patients within an 18-month period who underwent ventriculotomy or aneurysmectomy, at which time the presence or absence of thrombus was determined. From this group the M-mode and two-dimensional echocardiographic findings of eight patients with surgically proven left ventricular thrombi are reported. These patients underwent preoperative cardiac catheterization, biplane cineangiography and coronary arteriography. The echocardiographic findings of two patients with documented tumor involvement of the left ventricle are also discussed.

Echocardiographic Studies

All patients were studied with M-mode and two-dimensional real-time echocardiography. All echocardiographic studies were reviewed preoperatively and then retrospectively after the surgical confirmation of the mass. The echocardiograms were done within one month of the subsequent surgery.

The M-mode echocardiograms were done on a Smith-Kline Echoline 20A echocardiograph interfaced with an Irex 101 strip chart recorder. The two-dimensional real-time studies were performed with a Varian 3000 wide-angle, 80°, phased-array sector scanner. Both the M-mode and two-dimensional real-time recordings were done with the patient in the supine or 30° left lateral decubitus position. The M-mode echocardiograms were done by positioning the transducer at the fourth or fifth intercostal spaces at the left sternal border and directing the ultrasonic beam in the established manner to obtain a sweep of the left ventricle from apex to base.

The two-dimensional images were obtained in the long axis, or sagittal, plane by directing the echo sweep between the apex and base of the heart. Short axis, or transverse, views were obtained by directing the plane of sweep along a line drawn between the right hip and the left shoulder perpendicular to the long axis of the left ventricle.8 All patients were also studied by apex echocardiography, using the apex four chamber view and the apical frontal view. This

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