The Acute Hemodynamic Effects of Intravenous Verapamil in Coronary Artery Disease
Assessment by Equilibrium-gated Radionuclide Ventriculography

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SUMMARY The acute hemodynamic effects of an i.v. bolus of verapamil, 0.1 mg/kg or 0.06–0.075 mg/kg, were examined by serial radionuclide studies in 46 patients with coronary artery disease. In 20 patients with ejection fractions (EFs) > 35% (group 1A), verapamil, 0.1 mg/kg given over 1–1½ minutes, had a biphasic effect: a transient decrease in EF accompanied by increased left ventricular (LV) volumes and cardiac output equivalents; then, an overshoot of EF to values above control, accompanied by a decrease in peripheral vascular resistance and a drastic decrease in LV volumes, while cardiac output equivalent remained slightly elevated. In eight patients with EFs < 35% (group 1B), only the first effect on EF was noted. In 10 patients with EFs > 35% (group 2), verapamil, 0.06–0.075 mg/kg, exerted qualitatively similar but milder effects on hemodynamic function. Finally, verapamil, 0.1 mg/kg given more slowly, over 2–2½ minutes, produced no significant changes in EF or LV volumes in another eight patients (group 3). The acute effects of verapamil are thus both time-related and dose-dependent. They are also related to the baseline functional reserve of the left ventricle. This study documents that verapamil exerts a depressant effect on LV function. However, the transient nature of this depression and the quick recovery to normal or above-normal values indicate that verapamil, in the doses used in this study, is safe to use intravenously in patients with coronary artery disease.

VERAPAMIL has found ever-increasing uses in cardiology.1–3 The ability of verapamil to inhibit inward calcium flux through the so-called slow channels is believed to be its mechanism of action.4–6 Initial studies in cardiac muscle preparations and in experimental animals suggested that the calcium-inhibiting properties of verapamil make it an extremely powerful, negative inotropic agent.7, 8 Subsequent studies in man show a wide margin of safety in the use of the drug.9, 10 However, little is known about the effects of i.v. verapamil in patients with coronary artery disease, and fears have been expressed concerning its safety in these patients. We therefore examined the acute hemodynamic effects of an i.v. bolus of verapamil by gated radionuclide ventriculography11–15 in 46 ambulatory patients with coronary artery disease. Specifically, we evaluated the rapid and transient changes in the cardiovascular system in the first few minutes after the injection.

Methods

Subjects

Forty-one men and five women, ages 39–67 years (mean ± SD 56 ± 8 years), with angina pectoris secondary to coronary artery disease participated in this study. The diagnosis of coronary artery disease was based on documentation of previous acute myocardial infarction in 39 patients (anterior in 26, inferior in 10 and in both locations in three), followed in all by typical mild-to-moderate angina pectoris. In the seven other patients, the diagnosis of coronary artery disease was established by the presence of typical angina pectoris, brought on by effort and relieved by rest and nitroglycerin. The diagnosis of these seven patients was further documented by positive exercise tests and exercise-induced myocardial perfusion defects on the 201-thallium perfusion study, with a return to normal perfusion on equilibration 4 hours later. Cineangio-
graphic documentation of significant two- or three-vessel coronary disease was available in 10 patients. None of the patients had valvular regurgitation. One had associated aortic stenosis and one had undergone valve replacement. Three had documented left ventricular aneurysms. Twenty-eight patients were taking oral nitrates for angina pectoris; three were receiving propranolol for angina or for hypertension. Four patients received digoxin or diuretics for congestive heart failure and three were receiving amiodarone. Digoxin, diuretics and antiarrhythmic drugs were continued through the morning of the test to ensure a stable hemodynamic state before the test. All patients were tested in the postabsorptive state between 2:00 and 4:00 p.m., at least 6 hours after the last dose of oral nitrates, to minimize the degree of vasodilatation.

Testing Procedure

All patients gave informed consent and were studied in the nuclear medicine laboratory. An indwelling catheter was placed in an arm vein. The patient was then positioned supine on a comfortable table under the collimator and remained in this resting state for 30 minutes, in order to achieve steady state, as judged by a stable heart rate on the ECG and arm-cuff blood pressure. Care was taken that the patient remained quiet and awake during the entire procedure.

Two baseline studies were performed in the 45° left
tions were then serially obtained every 2 minutes after verapamil over the next 10 minutes. Blood pressure was repeatedly monitored with a sphygmomanometer during each phase of the study and the ECG was continuously recorded during the entire procedure.

Verapamil Injections

Verapamil was administered in a bolus of 0.1 mg/kg over 1–1½ minutes to 28 patients (group 1). In another group of 10 patients (group 2), a bolus of 0.06–0.075 mg/kg was administered within the same period of time to evaluate the effect of smaller doses of verapamil. In eight patients (group 3), a bolus of 0.1 mg/kg was injected over 2–2½ minutes.

Radionuclide Studies

Lyophilized pyrophosphate solution that contained 1.75 mg of Sn (Sorek NRC) was injected intravenously. Thirty minutes later, a solution of technetium-99m pertechnetate (TcO₄, Sorek NRC) was injected through the indwelling catheter in a dose of 30–35 mCi. After distribution of the radionuclide in the blood pool, data were collected up to a preset total of 3000 kilocounts, which usually took 2 minutes to acquire. All studies were performed using a commercial scintillation camera equipped with an all-purpose, medium resolution, medium-sensitivity, collimator (Elscint CE-1 and CCL-3).

The camera was positioned in the 45° left anterior oblique position, which included a 5–10° caudal tilt for maximal isolation of the left ventricle from the right ventricle and left atrium when necessary. The left anterior oblique position was adjusted for optimal visualization of the septum and separation of the left and right ventricles.

The data were acquired using the SYMA (Synchronized Multigated Acquisition) mode, using the R wave of the ECG fed into a minicomputer (Elscint Dykomette). The latter divides the RR interval into equal “frames” (16 for this study), derives the actual time for each frame and sums cardiac cycles at each corresponding frame to assemble a composite cardiac cycle. Each image frame has a spatial resolution of 32 x 32 channel elements (pixels) in the zoom x 2 mode.

The data were stored in a “floppy-diskette” and displayed on a color or black-and-white image display screen for visualization and photographic recording. Time-activity curves for the left ventricle at each stage of the study were generated by using a semiautomated left ventricular edge-detection technique developed by the manufacturer of the system. The operator places an initial region of interest (ROI) around the ventricle as visualized on the image display screen. The system allows frame-by-frame adjustment of the ROI to closely approximate the outline of the left ventricle as its size decreases from end-diastole to end-systole. Subtraction of background activity as contained in the original ROI is automatically performed by the computer. The final, background-corrected, left ventricular time-activity curve is then automatically calculated by the computer by using the second derivative method, with end-diastole represented by the highest number of counts at the early uppermost point in the curve, and end-systole represented by the lowest number of counts at the nadir of the curve.

At the beginning of acquisition, actual time per frame was determined by the computer, and the total number of cycles used for the acquisition of the 3000 kilocounts was registered for each study. Ejection fraction was calculated by the computer from background-corrected end-diastolic and end-systolic counts. To determine left ventricular radionuclide volume equivalents, formula 1 of Slutsky et al. was considered to be the simplest and most suitable for the purpose of this study. According to this formula,

\[ V = \frac{EDC \text{ or } ESC}{\text{No. of heart beats}} \times \frac{0.04 \text{ seconds}}{\text{actual time/frame}} \]

where \( V \) = volume, \( EDC \) = end-diastolic counts, \( ESC \) = end-systolic counts, heart beats = the number of cycles required for data acquisition, and actual time/frame = the time for acquisition of counts during each of the 16 frames.

The value obtained from this and other equations using radionuclide studies does not represent actual volumes in milliliters, but rather, radionuclide “volume equivalents” that are reasonably well correlated with contrast angiographic volumes. Because each patient served as his own control and changes in volumes and ejection fraction from baseline values were studied, the conclusions obtained by this equation are valid for this study.

Hemodynamic Equations

The following equations were used to determine relative changes from baseline in each patient.

Stroke volume equivalents (SVE) = EDVE - ESVE, where EDVE and ESVE = end-diastolic and end-systolic volume equivalents.

Cardiac output equivalent (COE) =

\[ (EDVE - ESVE) \times HR \]

where HR = heart rate measured at the beginning of each stage of the study.

Stroke work equivalent = SVE \times \overline{SAP},

where SAP = mean systemic arterial pressure, estimated by the equation

\[ \frac{\text{systolic BP - diastolic BP}}{3} + \text{diastolic BP}, \]

where BP = blood pressure.

Peripheral vascular resistance equivalent = \( \overline{\text{SAP}} / \text{COE} \)

All data were analyzed by the \( t \) test and analysis of variance for repeated measurements and are presented as mean ± SD.
Results

Baseline Hemodynamics

Ejection fraction was stable and reproducible in two consecutive radionuclide data acquisitions separated by 5 minutes after a rest of 30 minutes in 21 patients (mean 45.7 ± 17.4 and 46.1 ± 17.6, p > 0.1; the difference in ejection fraction for each patient did not exceed 3%). This, simultaneously with a stable heart rate and blood pressure, indicates that the patient had a stable baseline hemodynamic state before the verapamil injection. The patients were assigned to one of two groups according to whether their ejection fraction was above or below the cutoff point of 35%, and were analyzed separately to determine whether significant myocardial dysfunction influences the effect of verapamil on left ventricular function. This cutoff point of 35% was chosen arbitrarily.

Group 1A consisted of 20 patients with a mean ejection fraction of 55% ± 11 (range 35–76%); group 1B consisted of eight patients with a mean ejection fraction of 24% ± 5 (range 17–32%). The baseline end-diastolic and end-systolic radionuclide volume equivalents, stroke volume equivalent, cardiac output equivalents and stroke work equivalents are listed in table 1.

Effect of Verapamil on Heart Rate, Blood Pressure, Peripheral Vascular Resistance and PR Interval

Verapamil, 0.1 mg/kg over 1–1½ minutes, increased mean heart rate by 9.5% in group 1A and by 5.5% in group 1B and decreased systolic and diastolic blood pressure by 7% in group 1A and by 10–11% in group 1B (table 2). Systemic vascular resistance decreased by 25% in group 1A (p < 0.0005) and by 23% in group 1B (NS because of the small sample). Verapamil, 0.060–0.075 mg/kg, exerted a similar effect on heart rate, blood pressure and vascular resistance in group 2. Verapamil, 0.1 mg/kg given over 2–2½ minutes, decreased blood pressure 16% and increased heart rate 13% in group 3. No significant effect was noted on the PR interval.

Immediate Effects of Verapamil on LV Function

In the first radionuclide study performed in group 1A 2–4 minutes after the beginning of injection, verapamil, 0.1 mg/kg, decreased ejection fraction in 15 of 20 patients, did not affect it significantly in one patient and increased it immediately in four patients (fig. 1A). In group 1B, ejection fraction decreased slightly in five and did not change in three (fig. 1B). When the change in ejection fraction is expressed as a percentage of the baseline value, mean ejection fraction was initially reduced by 13% in both groups 1A and 1B (48 ± 13% vs 55 ± 11%, p < 0.005 in group 1A; 21 ± 5% vs 24 ± 5%, p < 0.005 in group 1B) (figs. 2 and 3; table 3). Mean end-diastolic and end-systolic left ventricular radionuclide volume equivalents were increased by 34% and 60% of their respective baseline values in group 1A (fig. 2) and by 28% and 34% respectively in group 1B (fig. 3). Nuclide stroke volume equivalent immediately increased by 14% from baseline (NS), cardiac output equivalent by 25%, and stroke work equivalent by 5% in group 1A (NS). These changes were smaller in group 1B.

Recovery Stage

The effects 4–6 minutes after administration of verapamil differed sharply between groups 1A and 1B. Immediately after the initial decline in ventricular function seen in the first 2–4 minutes after the beginning of the injection, ejection fraction not only immediately returned to its baseline value, but it also overshoot it and became “supernormal” in group 1A (62.7 ± 12% vs 55.0 ± 11%; p < 0.0005), with a gradual return to the normal value within the next 6–8 minutes after the beginning of the injection. The maximum ejection fraction thus represents a 14% increase above the control value (fig. 2). This increase in ejection fraction was observed in all 20 patients of group 1A (fig. 1A). In group 1B, in contrast, no overshoot was observed; after the initial decrease seen 2–4 minutes after beginning verapamil injection, ejection fraction returned gradually to normal within the next 6 minutes (fig. 1B).

Left ventricular volume equivalents also behaved differently in the recovery period. In group 1A, both end-diastolic and end-systolic volume equivalents decreased sharply to, or below, the control values 4–6 minutes after the onset of injection, while stroke volume and cardiac output equivalents became almost

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Hemodynamic Data for Groups 1A and 1B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1A (n = 20)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
</tr>
<tr>
<td>End-diastolic volume equivalent (units)</td>
</tr>
<tr>
<td>End-systolic volume equivalent (units)</td>
</tr>
<tr>
<td>Stroke volume equivalent (units)</td>
</tr>
<tr>
<td>Cardiac output equivalent (units)</td>
</tr>
<tr>
<td>Stroke work equivalent (units)</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Numbers in parentheses indicate the range. Volume, output and work equivalents were not compared between the two groups.

*p < 0.05.
normal (fig. 2). In group 1B, all values remained elevated for a longer time (4–6 minutes after onset of injection), with a later return to the baseline (fig. 3).

### Hemodynamic Effects of Verapamil in Group 2

Verapamil, of 0.06–0.075 mg/kg, produced an immediate decrease in ejection fraction in five of the 10 patients with ejection fractions greater than 35%. In each of these five, the same type of overshoot in ejection fraction noted in group 1A was observed. In the other five patients, ejection fraction did not change significantly. For the whole group, verapamil produced a modest (7%) but significant \((p < 0.005)\) decrease in the mean ejection fraction, from \(55.8 \pm 14.3\%\) to \(52.0 \pm 11.0\%\), followed by a similarly modest (6%) but significant overshoot, to \(59.3 \pm 13.9\%\) \((p < 0.005)\) (fig. 4). This dose produced changes in left ventricular volumes and cardiac output equivalents that were qualitatively similar to those produced by verapamil, 0.1 mg/kg, in group 1A, but they were less marked.

### Hemodynamic Effects in Group 3

When verapamil was given over 2–2½ minutes, no effect was noted on mean or individual ejection fraction (fig. 5). Left ventricular volume equivalents increased in two patients and decreased in six. Mean volume remained unchanged (diastolic volume equivalent 35.1 ± 19 vs 37.3 ± 20.5 units, NS; systolic volume equivalent 15.4 ± 8 vs 15.9 ± 9 units, NS), despite a 16% reduction in blood pressure and a 13% increase in heart rate.

### Discussion

**Technique**

Radionuclide ventriculography has been validated as a reliable, relatively noninvasive technique for investigating ventricular function. The technique is particularly well suited for studying the rapid changes in left ventricular dimensions and function that may occur after administering cardiocirculatory active drugs, without introducing the myocardial depression that is associated with radiopaque contrast techniques. Because of this variable, Ferlinz et al. waited 45 minutes after the first ventriculogram before repeating their study during verapamil infusion and 15 minutes after coronary angiography. Such delays are avoided by radionuclide ventriculography.

The aim of our study was to detect transient hemodynamic changes that might appear in the wake of a rapid injection of verapamil. Thus, we modified the technique of acquisition of nuclide counts so as to shorten the time of acquisition to a minimum while preserving as high as possible the number of counts available per frame in order to obtain reasonably accurate end-diastolic and end-systolic volumes. This was accomplished by injecting a large volume of radionuclide and by dividing the cardiac cycle into 16 frames only. This represented a compromise, to yield the shortest duration possible for each study while it increased by threefold the number of nuclide counts available for the end-diastolic and end-systolic frames from which ejection fraction was calculated. This technique thus gave results that were reproducible and sufficiently accurate. We did not attempt to determine the

### Table 2. Effects of Verapamil on Heart Rate and Blood Pressure

<table>
<thead>
<tr>
<th>Group 1A — 0.1 mg/kg verapamil in EF &gt; 35%</th>
<th>Control</th>
<th>Verapamil (2–4 min)</th>
<th>Recovery (4–6 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>73 ± 15</td>
<td>80 ± 16 (9.5%)*</td>
<td>78 ± 17 (6.8%)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>128 ± 20</td>
<td>118 ± 14 (−7%)*</td>
<td>121 ± 18 (−5%)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>84 ± 11</td>
<td>78 ± 11 (−7%)*</td>
<td>79 ± 12 (−5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 1B — 0.1 mg/kg verapamil in EF &lt; 35%</th>
<th>Control</th>
<th>Verapamil (2–4 min)</th>
<th>Recovery (4–6 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>70 ± 10</td>
<td>74 ± 13 (5.5%)*</td>
<td>71 ± 13 (1%)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>108 ± 19</td>
<td>97 ± 15 (−10%)*</td>
<td>101 ± 14 (−6.5%)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>73 ± 14</td>
<td>65 ± 12 (−11%)*</td>
<td>72 ± 13 (−1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2 — 0.06–0.075 mg/kg verapamil in EF &gt; 35%</th>
<th>Control</th>
<th>Verapamil (2–4 min)</th>
<th>Recovery (4–6 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>69 ± 13</td>
<td>74 ± 12 (7%)*</td>
<td>71 ± 12 (2.8%)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>139 ± 21</td>
<td>126 ± 23 (−9.3%)*</td>
<td>129 ± 21 (−7.7%)*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>83 ± 9</td>
<td>76 ± 7 (−8.4%)*</td>
<td>78 ± 10 (−6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 3 — 0.1 mg/kg verapamil given over 2–2½ minutes</th>
<th>Control</th>
<th>Verapamil (2–4 min)</th>
<th>Recovery (4–6 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>67 ± 10</td>
<td>76 ± 10 (13%)*</td>
<td>70 ± 11 (4%)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>132 ± 17</td>
<td>110 ± 10 (−16%)*</td>
<td>130 ± 15 (−0.1%)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>85 ± 5</td>
<td>73 ± 7 (−15%)*</td>
<td>79 ± 5 (−7%)</td>
</tr>
</tbody>
</table>

*p < 0.05 vs control.  
†p < 0.005 vs control.  
Abbreviation: BP = blood pressure.
effect of verapamil on segmental wall motion because we could not obtain enough counts by our technique. Formula 1 of Slutsky et al. does not give the absolute radionuclide volume values obtained by using their formula 4. However, our aim was to determine whether relative changes in ventricular volumes occurred after verapamil. We therefore used formula 1 of Slutsky et al. because it does not require additional counting of plasma radioactivity.

**Verapamil Injection**

The hemodynamic effects of i.v. verapamil can be

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**TABLE 3. Serial Effects of Verapamil, 0.1 mg/kg, on Left Ventricular Performance**

<table>
<thead>
<tr>
<th>Group IA — EF &gt; 35%</th>
<th>Baseline</th>
<th>2–4 min</th>
<th>4–6 min</th>
<th>6–8 min</th>
<th>8–10 min</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>55.0 ± 11</td>
<td>48.3 ± 13</td>
<td>62.7 ± 12</td>
<td>59.0 ± 13</td>
<td>57.0 ± 12</td>
<td>0.0068</td>
</tr>
<tr>
<td>EDVE (units)</td>
<td>41.7 ± 12.6</td>
<td>55.9 ± 21</td>
<td>39.6 ± 15</td>
<td>41.7 ± 13</td>
<td>41.8 ± 10.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>ESVE (units)</td>
<td>18.4 ± 8.5</td>
<td>29.4 ± 17.6</td>
<td>14.8 ± 8.9</td>
<td>16.5 ± 9.2</td>
<td>16.8 ± 7.2</td>
<td>0.004</td>
</tr>
<tr>
<td>SVE (units)</td>
<td>23.0 ± 7.5</td>
<td>26.3 ± 7.9</td>
<td>25.2 ± 9.3</td>
<td>24.8 ± 7.8</td>
<td>24.5 ± 7.9</td>
<td>NS</td>
</tr>
<tr>
<td>COE (units)</td>
<td>1724 ± 830</td>
<td>2153 ± 1036</td>
<td>2049 ± 1082</td>
<td>1860 ± 802</td>
<td>1764 ± 739</td>
<td>0.001</td>
</tr>
<tr>
<td>SWE (units)</td>
<td>2282 ± 777</td>
<td>2400 ± 757</td>
<td>2273 ± 843</td>
<td>2306 ± 741</td>
<td>2305 ± 799</td>
<td>NS</td>
</tr>
<tr>
<td>PVRE (units)</td>
<td>6.80 ± 2.80</td>
<td>5.09 ± 2.22</td>
<td>5.63 ± 2.56</td>
<td>—</td>
<td>—</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group IB — EF &lt; 35%</th>
<th>Baseline</th>
<th>2–4 min</th>
<th>4–6 min</th>
<th>6–8 min</th>
<th>8–10 min</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>24.0 ± 6</td>
<td>21.0 ± 5</td>
<td>22.7 ± 5</td>
<td>24.0 ± 6</td>
<td>25.0 ± 7</td>
<td>0.0068</td>
</tr>
<tr>
<td>EDVE (units)</td>
<td>57.0 ± 24</td>
<td>73.0 ± 32</td>
<td>70 ± 23</td>
<td>57 ± 21</td>
<td>59 ± 20</td>
<td>0.005</td>
</tr>
<tr>
<td>ESVE (units)</td>
<td>44.0 ± 21</td>
<td>59.0 ± 30</td>
<td>54.0 ± 21</td>
<td>44.0 ± 18</td>
<td>45.0 ± 17</td>
<td>0.005</td>
</tr>
<tr>
<td>SVE (units)</td>
<td>13.0 ± 3.5</td>
<td>14.0 ± 5</td>
<td>16.0 ± 3.6</td>
<td>13.0 ± 4</td>
<td>14.0 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>COE (units)</td>
<td>979 ± 330</td>
<td>1149 ± 373</td>
<td>1197 ± 299</td>
<td>1070 ± 468</td>
<td>1068 ± 496</td>
<td>NS</td>
</tr>
<tr>
<td>SWE (units)</td>
<td>1126 ± 245</td>
<td>1148 ± 342</td>
<td>1248 ± 257</td>
<td>1127 ± 406</td>
<td>1176 ± 455</td>
<td>NS</td>
</tr>
<tr>
<td>PVRE (units)</td>
<td>9.19 ± 4.78</td>
<td>7.08 ± 2.29</td>
<td>7.05 ± 1.51</td>
<td>—</td>
<td>—</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: EF = ejection fraction; EDVE = end-diastolic volume equivalent; ESVE = end-systolic volume equivalent; SVE = systolic volume equivalent; COE = cardiac output equivalent; SWE = stroke work equivalent; PVRE = peripheral vascular resistance equivalent.
FIGURE 2. Percent changes in ejection fraction (EF), left ventricular end-diastolic and end-systolic volume equivalents (EDVE and ESVE), stroke output equivalent (COE), and stroke work equivalent (SVE) induced by verapamil in group IA. Symbols are as in figure 1. Immediately after verapamil, depression of left ventricular (LV) function is manifest by decreased EF and increased dimensions. Recovery of function appears shortly thereafter, as shown by overshoot of EF and prompt return of LV volumes to (or below) control values. The increase in COE and SVE does not reflect the depressed LV function.

FIGURE 3. Percent changes in hemodynamic variables induced by verapamil in group IB. Symbols are as in figure 1. The depression of left ventricular (LV) function seen in group IA is also observed here (decreased ejection function (EF) and increased LV dimensions) immediately after verapamil. The overshoot in LV function seen in group IA, however, is absent in group IB, and EF and volumes return gradually to control. Cardiac output and stroke volume equivalents (COE and SVE) increase and thus fail to reflect the depressed LV function. SWE = stroke work equivalent.

stable hemodynamic effects. Ross and Jorgensen suggested that cumulative effects appear during continuous infusion.26

Hemodynamic Effects of Verapamil

Verapamil inhibits inward calcium flux through the so-called slow channels.4, 6, 27 The major cardiovascular results of this property are decreased conduction velocity through the atrioventricular junction,4 relax-
Figure 4. Percent changes in hemodynamic variables induced by verapamil, 0.06–0.075 mg/kg, in group 2. Symbols are as in figure 1. More modest changes in ejection fraction (EF) and volumes than in group 1A are observed. SWE = stroke work equivalent; SVE = stroke volume equivalent; COE = cardiac output equivalent; LV = left ventricular.

Ventricular function and volume change with verapamil.34–36 The decreased conduction velocity helps to decrease the ventricular rate in atrial fibrillation28, 29 and stop paroxysmal supraventricular tachycardia.30 Relaxation of smooth muscle is useful for the treatment of hypertension and angina pectoris.1, 2 Depression of myocardial contractility has more recently been applied to the treatment of idiopathic hypertrophic subaortic stenosis.1–3

Hazards associated with verapamil arise from its capability to decrease the rate of impulse formation in the sinoatrial node and to produce excessive atrioventricular block.6 It can also cause severe hypotension as a result of both its vasodilating and myocardial depressant activity, which may lead to congestive heart failure.6 In this study, none of these hazardous effects was observed when verapamil was given in a bolus of 0.1 mg/kg over 1–1½ minutes. This dose is slightly greater than the dose of 5 mg usually given as a single bolus to patients with arrhythmias, and the time of administration is slightly shorter than the usual 2–5 minutes.6, 28, 30 The fact that this dose was well tolerated by 28 patients, including eight with moderately to extremely reduced ejection fraction, indicates that verapamil is relatively safe for patients with coronary artery disease, even in the absence of compromised ventricular function, despite its depressant properties on the myocardium. Our study thus supports recent reports.23–25, 31, 32 The safety of verapamil in the doses used here remains to be determined in patients with acute left ventricular dysfunction.

The hemodynamic effects of verapamil in man have been investigated during catheterization.23–25, 31–34 Conflicting results have been reported, probably because of the varying laboratory conditions, differing subsets of subjects, methods of administration of verapamil and methods of quantitation. Cardiac output has been reported to decrease,35 increase,24, 25, 34 or not change,9, 10 and stroke volume has been reported either not to change6 or to increase.24, 25 Left ventricular end-diastolic pressure, pulmonary wedge pressure and left atrial pressure have been reported not to change16, 34 or to increase.5, 24, 25, 33 Left ventricular or aortic dP/dt has been reported to decrease10, 25, 33 or not to change,9 while mean velocity of circumferential fiber shortening has been reported to increase24 and ejection fraction not to change10 or to increase.24 Thus, the reported effects of verapamil on hemodynamic indexes of left ventricular function vary from study to study.

Ferlinz et al.23 examined left ventricular dimensions by ventriculography in 20 patients with coronary artery disease. The end-diastolic volume did not change and end-systolic volume decreased (resulting in increased ejection fraction) when examined 20–28 minutes after beginning of a continuous infusion. M-mode echocardiographic end-diastolic and end-systolic dimensions (and, therefore, ejection fraction), however, did not change in five patients with coronary artery disease studied 5 minutes after a bolus of verapamil. Because of technical limitations, ventricular volumes have not previously been examined within the first few minutes of verapamil injection, at a time when the most rapid and dramatic hemodynamic changes in the cardiovascular system can be expected to take place. More recently, Vlieistra et al.34 studied diastolic volumes by left ventriculography during continuous verapamil infusion and found that they increased.34

Radionuclide techniques have been used to study the acute effects of i.v. verapamil.35, 36 In two studies, verapamil was given in a continuous infusion after a bolus injection. In the first study,35 no significant change was noted in pulmonary capillary wedge pressure and ejection fraction at rest, while verapamil prevented the fall in ejection fraction noted during atrial pacing. In the
second study, there was an insignificant increase in mean ejection fraction, while stroke index and pulmonary capillary wedge pressure rose significantly and peripheral vascular resistance fell in a group of 22 patients with good myocardial reserve (as judged by pulmonary capillary wedge pressure of less than 12 mm Hg). Three patients with congestive heart failure showed hemodynamic deterioration. Neither of the studies entirely answers the question we asked at the onset: What are the acute effects of a bolus injection of the type given to patients with an arrhythmia?

Our attention was therefore directed at the short interval immediately after the bolus injection and preceding even the earliest hemodynamic measurements reported in the literature. Our results demonstrate that verapamil exerts effects that are time-related and dose-dependent and that differ according to the initial quality of left ventricular function and reserve as defined by an ejection fraction above or below 35%.

Thus, in patients with reasonable or good left ventricular function (ejection fraction above 35%), a bolus of 0.1 mg/kg has a dual and biphasic effect on the cardiovascular system. In the first 2–4 minutes after the beginning of injection (30–90 seconds from the end of injection), depression of left ventricular function is the first evident effect, as shown by the transient but marked increases in left ventricular end-diastolic and end-systolic radionuclide volumes and by a reduced ejection fraction. However, as peripheral vasodilation develops, systemic vascular resistance and blood pressure decrease. This leads to a compensatory increase in sinus rate. As a result of the unloading effect of the peripheral vasodilation, and possibly also because of sympathetically mediated increases in myocardial contractility, ejection fraction increases dramatically to levels above the control values in the next 1–2 minutes (4–6 minutes after onset of injection), corresponding more or less to the period studied by Singh and Roche and Rydén and Saetre, while both end-diastolic and end-systolic volumes decrease sharply to values close to or even below baseline values. A temporary verapamil-induced decrease in venous return may also play a role at this stage, as the drug also suppresses mechanical activity in certain venous beds.

During both the first phase (depressed ventricular function) and the second phase (enhanced ventricular function) of this dual effect of verapamil, cardiac output increases markedly, primarily because of the increased heart rate. Stroke work and stroke volume apparently increase transiently during the first phase (NS).

Compared with patients with reasonably preserved left ventricular function, the cardiovascular system of patients with an ejection fraction of less than 35% reacts differently to verapamil. Ejection fraction is initially suppressed proportionately to the same extent, but there is no overshoot as seen when myocardial reserve is maintained. Left ventricular volumes become less enlarged, but remain enlarged longer. This suggests that left ventricular myocardial function remains significantly depressed for a longer time and, despite an equally decreased peripheral vascular resistance (23% in group 1B vs 25% in group 1A), the ventricle cannot improve its ejecting capability quickly. Despite this myocardial depression, cardiac output
increased. This apparently paradoxical situation was also observed in group 1A (fig. 3) in the first phase of ventricular depression. These observations confirm again that conclusions that are drawn from stroke volume and cardiac output data alone may be misleading insofar as ventricular function in response to verapamil and other drug interventions is concerned. For example, Ross and Jørgensen concluded that verapamil in doses as high as 0.25 mg/kg does not depress the heart, and that its hypotensive effects are due only to peripheral vasodilatation in anesthetized cats.26 Ferlinz et al.23 found improved cardiac output, stroke volume, ejection fraction and mean velocity of circumferential fiber shortening in man, while LV end-diastolic volume did not change, and were therefore reluctant to attribute a significant myocardial depressant effect to verapamil, and postulated that the slightly increased left ventricular end-diastolic pressure and pulmonary wedge pressure were caused by decreased compliance.25 However, their method enabled them to study left ventricular volumes only 45 minutes after the first ventriculogram, 20–29 minutes after a verapamil bolus, at a time when the initial left ventricular dilatation seen so clearly by our radionuclide method would have vanished long before because of decreased afterload.

Thus, verapamil in the doses and time of injection used clinically indeed depresses left ventricular function in man, as shown by the increased volumes demonstrated in this study, by increased end-diastolic pressure4 23-25, 36 and by decreased dP/dt.33 However, this depressant effect is short-lived and evanescent in the heart with reasonably preserved myocardial reserve, and is somewhat more prolonged in the presence of severe left ventricular dysfunction when doses of 0.1 mg/kg are used. In doses of 0.6–0.75 mg/kg, which are even closer to the frequently used standard bolus of 5 mg, or when the larger dose of 0.1 mg/kg is given more slowly, the effects of verapamil are even less pronounced and more short-lived. Also of interest, peripheral vasodilatation is still demonstrable after slow injection of verapamil, although the myocardial depression is no longer evident (group 3).

In conclusion, rapid administration of a bolus of verapamil in patients with coronary artery disease is followed by a series of interrelated adjustments that lead to varying hemodynamic results, depending on the underlying cardiovascular state of the particular patient tested. The effects are a combination of marked but transient left ventricular depression and decreased afterload. The most important overall effect of verapamil on the cardiovascular system as an integrated system appears to be an improvement in function, brought about by decreased resistance to ventricular emptying and, perhaps, by a sympathetically mediated increase in myocardial contractility, provided the sympathetic reflex mechanisms are intact. Verapamil is well tolerated in bolus injections, even in severe left ventricular dysfunction in the doses used here. We cannot extrapolate our data to larger doses or to continuous infusions, because cumulative effects may produce different hemodynamic consequences. Similarly, the safety of an i.v. bolus of verapamil in acute left ventricular decompensation must be determined by a similar investigational protocol.

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Kinetics and Imaging of Indium-111-labeled Autologous Platelets in Experimental Myocardial Infarction

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SUMMARY The kinetics of accumulation and the external imaging patterns of indium-111-labeled platelets infused in a dog model of left anterior descending coronary artery occlusion with reperfusion were studied. The effects of infarct age and regional residual myocardial blood flow upon platelet accumulation were quantified, and the capacity of indium-111 platelets to image the experimental infarction was evaluated qualitatively. The endocardial accumulation of indium-111 platelets occurred primarily in infarct zones with residual blood flow <0.6 times normal and was maximal (24.98 ± 2.76 times normal) in the lowest blood flow zone (<0.1 times normal). Indium-111 platelet accumulation in the epicardium occurred in the regions with blood flow <0.6 times normal and was maximal (17.83 ± 1.20 times normal) in the lowest blood flow zone (<0.1 times normal). The maximal endocardial and epicardial platelet accumulation occurred 24 hours after reperfusion and was significantly decreased at 48 hours. In vivo cardiac images revealed discrete areas of increased myocardial radioactivity uptake in the anterior wall of dogs 24 hours after reperfusion. All images 48 hours after reperfusion were negative. Thus, in the experimental setting, indium-111 platelets allow quantification of platelet accumulation after myocardial infarction at a tissue level and provide a noninvasive means of in vivo imaging of reperfused infarcted myocardium.

PLATELET accumulation in areas of myocardial infarction has been demonstrated histologically and with chromium-51 (51Cr)-labeled platelets.1 2 Indium-111 (111In)-labeled platelets have been used to identify left ventricular thrombi,3 coronary bypass graft thrombi4 and acute coronary artery thrombi.5 The ability to image the inflammatory response to acute myocardial infarction in dogs and man using 111In-labeled leukocytes has been demonstrated.6 7 Recent studies also suggest the crucial role that platelet aggregate microemboli may play in infarct extension2 8 and fatal ventricular arrhythmias.9 Definition of the kinetics of platelet accumulation into acute infarct zones is important because platelet inhibitors may limit the degree of ischemic necrosis10 and may prevent fatal ventricular arrhythmias resulting from acute myocardial infarction.11 The development of the technique for 111In labeling of platelets provides a direct means for assess-

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