Effects of Verapamil on Myocardial Performance in Coronary Disease

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SUMMARY Verapamil, a calcium antagonist, has been used extensively for treatment of cardiac arrhythmias. Concern persists, however, that it may seriously depress myocardial function in cardiac patients. To investigate this possibility, 20 patients with coronary artery disease (CAD) but no heart failure were given intravenous verapamil (0.1 mg/kg bolus, followed by 0.005 mg/kg/min infusion), and studied hemodynamically and angiographically.

Verapamil markedly lowered mean aortic pressure (94 ± 17 to 82 ± 13 mm Hg, p < 0.0005) and systemic vascular resistance (1413 ± 429 to 1069 ± 235 dyn-sec-cm⁻², p < 0.0005). Simultaneously, all indices of left ventricular (LV) performance greatly improved: cardiac index rose from 2.8 ± 0.6 to 3.1 ± 0.7 l/min/m² (p < 0.0005), mean velocity of circumferential fiber shortening increased from 0.85 ± 0.39 to 0.97 ± 0.46 cm/sec (p < 0.01), and ejection fraction improved from 55 ± 16 to 61 ± 18% (p < 0.01). No significant changes were noted in the heart rate before and after verapamil administration, and verapamil did not worsen the extent of LV asynergy in the majority of patients.

In patients with CAD, the intrinsic negative inotropic effect of verapamil is of negligible importance because its potent vasodilatory properties more than compensate for any intrinsic decrease in LV contractility, and thereby improve the overall cardiac function.

VERAPAMIL (ipoveratril) is a papaverine derivative with multiple effects on the cardiovascular system. Although it was initially believed to be a β blocker, it is a calcium antagonist which selectively blocks the slow channel by inhibiting the slow inward ionic current carried by calcium (and possibly sodium) ions.

Verapamil has been used extensively as an antiarrhythmic and antianginal agent, and preliminary trials have been conducted to determine if it can effectively reduce the size of an acute infarct. In spite of very promising preliminary results in most areas of application, the unquestionable acceptance of verapamil for clinical use and the Food and Drug Administration approval for its distribution in the US have been hampered by a fear that verapamil's intrinsic negative inotropic effects may preclude its use in patients with serious cardiac disorders, especially patients with coronary artery disease (CAD), because both verapamil and ischemia interfere with the movement of calcium ions to the contractile proteins of the myocardial cells, and could in theory synergistically impede calcium transport, causing a profound depression of myocardial contractility.

This study was undertaken to examine the effects of verapamil on patients with CAD who are theoretically at a special risk if this agent is administered, to determine what changes in left ventricular (LV) performance occur in such patients, and to assess what adverse cardiovascular effects the drug may produce in commonly accepted therapeutic doses.

Materials and Methods

For this study, we selected 20 consecutive patients with chronic angina pectoris who were found, upon cardiac catheterization for diagnostic purposes, to have significant CAD. A clinical profile for the entire patient population is presented in table 1. All gave informed consent and underwent routine diagnostic cardiac catheterization studies, which, in our laboratory, include complete left and right hemodynamic evaluation, cardiac output (CO) determined by the indocyanine green indicator-dilution technique, selective left ventriculography, and coronary arteriography. All patients were in normal sinus rhythm; none had systemic hypertension, significant valvular or congenital lesions, or history of congestive heart failure. Patients with clinically significant renal or hepatic failure, left bundle branch block, sinus bradycardia, systolic blood pressure below 90 mm Hg, or recent myocardial infarction were excluded from the study. None of the patients were excluded from the study because of adverse side effects caused by verapamil, or because complete hemodynamic and volumetric evaluation could not be performed for technical reasons.

Some patients were receiving cardiovascular medications, but in each instance all drugs except sublingual nitroglycerin were discontinued at least 5 days before the study without any clinical evidence of deterioration of cardiac function or increase in chest pain. None of the patients had to take nitroglycerin for at least 10 hours before cardiac catheterization.

After the first ventriculogram and coronary arteriography, 0.1 mg/kg of verapamil was given as a bolus intravenously over a 2-minute period; the intra-

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venous verapamil infusion of 0.005 mg/kg/min was started with a Harvard infusion pump immediately after the bolus injection and continued until all data were collected. The mean total dose of verapamil was 17.2±2.8 mg, and the length of the infusion averaged 23±5 minutes. Forty-five minutes after the first ventriculography (and 15 minutes after coronary angiography), the second left ventriculogram was performed during verapamil infusion. We allowed 45 minutes to elapse between first and second ventriculograms in order to eliminate the pharmacological effects of the contrast medium on myocardial contractility,36,37 and we allowed 15 minutes to elapse after the coronary cineangiography in order to avoid the possible effects of transient reactive hyperemia on myocardial contractility.32,33

Both selective left ventriculograms were obtained using a #8 Cordis pigtail catheter positioned in the left ventricle. We injected 45–50 ml of 76% meglumine sodium diatrizoate (Renografin 76) over a 3-second interval. Left ventriculograms in 30° right anterior oblique position were recorded at 64 frames/sec on 35 mm Ilford Cinegram F film with a Philips 9-inch image intensifier. Two independent observers analyzed only the first four beats after complete opacification. If an infrequent premature ventricular contraction was detected, at least two successive normal sinus beats (after the premature beat) had to occur before a frame was selected for analysis.

A modification34 of the area-length method of Dodge35 was used in the analysis of all LV volumes. End-diastolic volume index (EDVI), end-systolic volume index (ESVI), stroke volume index (SVI), and ejection fraction (EF = SVI/EDVI) were calculated for each patient.

Each ventriculogram was interpreted qualitatively for vigor and uniformity of contractions at all points along the ventricular outline. A quantitative analysis was performed by combining previously described approaches,36,37 and using internal thoracic structures (spine, rib margins, or a diaphragm) as fixed references. End-systolic (ES) and end-diastolic (ED) images were fitted with a longitudinal axis (obtained by dividing the images with a connecting line between the bisected aortic valve and the ventricular apex) and six hemiaxes (perpendicular to the longitudinal axis, which was divided into four equal segments). The longitudinal axis and each hemixis were then measured and normalized as percent decrease (or increase) in length from the ED dimension:

\[
\text{\% shortening} = \frac{\text{ED axis} - \text{ES axis}}{\text{ED axis}} \times 100.
\]

A hypokinetic zone was defined when <25% hemiaxis shortening was observed in the initial ventriculogram.38 According to the classification of Herman et al.,39 hypokinesis represented the mildest form of asynergy, followed by increasingly more pronounced LV wall-motion abnormalities when akinesis and dyskinesis were encountered. An increase in shortening ≥10% after administration of verapamil was considered an improvement in an asynergic segment,39 and a decrease ≥10% a deterioration.

CO, arterial-venous difference, and pressure data were collected just before each ventriculogram. CO was determined with the Lyons indocyanine green indicator-dilution, computer by averaging four sequential measurements. All pressures — aortic (AP) and pulmonary artery (PAP), systolic, diastolic and mean; right and left ventricular systolic and end-diastolic; mean right atrial (RAP); and mean pulmonary artery wedge (PAWP) were measured using Statham model P23Db strain gauges and recorded with an Electronics for Medicine DR-12 Simultrace recorder over three full respiratory cycles. Systemic pressure was recorded 1, 3, 5, 10, and 15 minutes after the verapamil bolus was administered. Heart rate was monitored throughout the study. In addition, systemic vascular resistance (SVR = [mean AP — mean RAP]/CO), pulmonary vascular resistance (PVR = [mean PAP — mean PAWP]/CO), and mean velocity of circumferential fiber shortening (Vcf = (ED — ES)/ED × ejection time), where ED and ES are left ventricular minor axes in end-diastole and end-systole)40 were calculated for each patient.

All coronary cineangiograms were of high technical quality. Significant CAD was considered to be present only when there was at least a 75% occlusion of at least one of the three coronary arteries, and when this observation was confirmed by two independent observers.

All data were analyzed using the t test41 for paired variables.

**Results**

The complete mean hemodynamic and volumetric data obtained before and after verapamil administration are given in table 2, and a summary of key cardiovascular findings for each patient in table 3. Verapamil markedly lowered AP and SVR. The decrease in AP occurred almost immediately after bolus administration, and was then effectively main-
Table 2. Cardiovascular Changes Induced by Administration of Verapamil

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Verapamil (Mean ± SD)</th>
<th>After Verapamil (Mean ± SD)</th>
<th>Significance (p)</th>
</tr>
</thead>
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<tr>
<td>LVEDP (mm Hg)</td>
<td>12 ± 4</td>
<td>14 ± 4</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>4 ± 2</td>
<td>7 ± 2</td>
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<tr>
<td>Syst. AP (mm Hg)</td>
<td>133 ± 25</td>
<td>114 ± 17</td>
<td>&lt;0.0005</td>
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<tr>
<td>Diast. AP (mm Hg)</td>
<td>71 ± 11</td>
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<td>&lt;0.0005</td>
</tr>
<tr>
<td>Mean AP (mm Hg)</td>
<td>94 ± 17</td>
<td>82 ± 13</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Mean PAP (mm Hg)</td>
<td>15 ± 4</td>
<td>17 ± 3</td>
<td>&lt;0.0025</td>
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<tr>
<td>Mean PAPW (mm Hg)</td>
<td>3 ± 2</td>
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<td>&lt;0.0005</td>
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<tr>
<td>SVR (dyne-sec-cm⁻¹)</td>
<td>1,413 ± 429</td>
<td>1,069 ± 235</td>
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<tr>
<td>PVR (dyne-sec-cm⁻¹)</td>
<td>100 ± 58</td>
<td>112 ± 46</td>
<td>NS</td>
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<tr>
<td>(A-V)O₂ (vol %)</td>
<td>3.92 ± 0.53</td>
<td>3.17 ± 0.62</td>
<td>&lt;0.0005</td>
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<tr>
<td>CI (l/min/m²)</td>
<td>2.8 ± 0.6</td>
<td>3.1 ± 0.7</td>
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<tr>
<td>HR at CI (beats/min)</td>
<td>74 ± 12</td>
<td>75 ± 12</td>
<td>NS</td>
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<tr>
<td>Vcf (circ/sec)</td>
<td>0.85 ± 0.39</td>
<td>0.97 ± 0.46</td>
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<td>HR at V-gram (beats/min)</td>
<td>71 ± 16</td>
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<td>EDVI (ml/m²)</td>
<td>110 ± 34</td>
<td>111 ± 34</td>
<td>NS</td>
</tr>
<tr>
<td>ESVI (ml/m²)</td>
<td>52 ± 29</td>
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<td>SVI (ml/m²)</td>
<td>57 ± 12</td>
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<td>EF (%)</td>
<td>55 ± 16</td>
<td>61 ± 18</td>
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Abbreviations: AP = arterial pressure; (A-V)O₂ = arterial-venous difference; CI = cardiac index; EF = ejection fraction; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; NS = not significant; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RVEDP = right ventricular end-diastolic pressure; SVI = stroke volume index; SVR = systemic vascular resistance; V-gram = cineangiographic ventriculogram; Vcf = mean velocity of circumferential fiber shortening.

Table 3. Summary of Key Cardiovascular Findings for Each Patient

<table>
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<tr>
<th>Patient no.</th>
<th>LVEDP (mm Hg) Before V</th>
<th>LVEDP (mm Hg) After V</th>
<th>Mean AP (mm Hg) Before V</th>
<th>Mean AP (mm Hg) After V</th>
<th>SVR (dyne-sec-cm⁻¹) Before V</th>
<th>SVR (dyne-sec-cm⁻¹) After V</th>
<th>CI (l/min/m²) Before V</th>
<th>CI (l/min/m²) After V</th>
<th>Vcf (circ/sec) Before V</th>
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<td>3.1</td>
<td>0.85</td>
<td>0.97</td>
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Abbreviations: AP = arterial pressure; CI = cardiac index; EF = ejection fraction; LVEDP = left ventricular end-diastolic pressure; SVR = systemic vascular resistance; V = verapamil; Vcf = mean velocity of circumferential fiber shortening.
administration of verapamil (from 37 ± 2 to 40 ± 10% and 0.45 ± 13 to 0.52 ± 0.20 circ/sec, respectively).

Eighteen patients (90%) had regional disorders of LV contractility, delineated by abnormal shortening of 49 hemiaxes. In each case, the area of asynergy was supplied by a critically narrowed coronary artery. After administration of verapamil, 17 of 49 asynergic segments improved (35%), 17 remained unchanged (35%), and eight worsened (16%). In addition, seven previously normal segments (14%) became asynergic after verapamil. Overall, 70% of all asynergic (or potentially asynergic) segments therefore improved or remained the same after the drug was administered, while only 30% deteriorated further (fig. 3).

**Discussion**

The reproducibility of the angiographically determined volumes and EF determined from the two left ventriculograms obtained during the same catheterization and at a comparable hemodynamic state have been examined previously in our laboratory. In accord with the data reported by other investigators,42 no significant difference was found between volumes and EF determined from the two sequential studies. Furthermore, McAnulty et al.43 have shown that sequential ventriculograms without any pharmacological interventions reproduce areas of LV asynergy that are constant in site and magnitude, and can therefore be used to study the effects of medical and surgical treatment on LV wall motion abnormalities.

We administered a fairly large intravenous dose of verapamil to all patients (17.2 ± 2.8 mg). Because the intrinsic myocardial depressant effect of verapamil is dose-related,44 45 the drug was given in these relatively high quantities to elicit the greatest deterioration of the LV function that could be produced with
therapeutic doses of verapamil. Verapamil was given as an intravenous infusion (after the bolus was administered) to assure the even action of the drug throughout the experiment: The half-life of verapamil given as a bolus intravenously is very short, and its effect is greatly attenuated within 10 minutes after its administration.

Verapamil produced a highly significant drop in AP and SVR after the bolus was injected, and then maintained the reduced mean AP with only minor fluctuations throughout the duration of the infusion. This decrease in blood pressure is due to the direct relaxant action of verapamil on the arterial and venous smooth muscle, an effect which has been repeatedly demonstrated in vitro and in vivo. A drop of this magnitude in blood pressure should, however, elicit reflex tachycardia. A number of studies report an increase in heart rate after verapamil, but other investigators have failed to observe any significant changes in heart rate following administration of verapamil. Even though we monitored the heart rate continuously, we could detect no appreciable changes in this parameter. This lack of agreement between various studies may be due, in part, to different investigators using different doses of verapamil. More importantly, verapamil is not just a vasodilator: It also depresses the atrioventricular, and probably sinoatrial conduction, so that in an isolated heart (where reflex tachycardia can not interfere) it produces bradycardia. The net effect of verapamil on the heart rate in an intact organism is therefore determined by the balance that a given dose of this drug exerts on the two mechanisms that, respectively, speed or slow the heart.

The influence of verapamil on CO is controversial. Different investigators have observed that it may decrease, may not change, or increase CO. These findings are divergent (at least partially) because different doses of verapamil are used in different studies. Our study proves that verapamil markedly increases CO when given to heart patients in therapeutic doses, a response that can be expected from any vasodilator capable of significantly reducing aortic impedance. Furthermore, the intrinsic negative inotropic effect of verapamil in therapeutic doses is not great enough to influence substantially its action as a vasodilator; otherwise, a decrease in cardiac output would be detected.

There is almost universal agreement that verapamil produces a significant decrease in LV contractility. Yet, none of the studies conducted so far have investigated the effect of verapamil on left ventricular ejection fraction and Vcf, which are commonly accepted to be the most sensitive indices of ventricular performance. While they are not pure indices of ventricular contractility, both EF and Vcf increase markedly after verapamil, indicating that LV performance improves rather than deteriorates when this drug is given in therapeutic doses. A possible explanation for this unexpected finding could be that verapamil's potent coronary vasodilating action increases blood flow to ischemic myocardium, thereby improving contractility, although one early, noninvasive study concluded that verapamil fails to augment coronary blood flow when given to patients with CAD. More importantly, verapamil acts as a peripheral vasodilator which can improve LV function by reducing impedance to ventricular ejection, thereby increasing EF and Vcf. Similar findings have been reported with other potent peripheral vasodilators, and in one animal study which investigated the effect of verapamil on the maximum rate of change of LB pressure-integrated isometric tension index (dp/dt/IIT). Clearly, the intrinsic negative inotropic effect of verapamil in therapeutic doses is very weak, and can be easily overcome by the drug's potent properties as a peripheral vasodilator.

The mean PAWP and the LVEDP increased after administration of verapamil, while there was a substantial, concomitant decrease in afterload. Because verapamil did not augment LV end-diastolic volume, it can be postulated that the increase in LVEDP represents a verapamil-induced decrease in LV compliance. The increase in LV filling pressures is reflected in the hemodynamics of the right heart, as PAP, RAP and right ventricular end-diastolic pressure all exhibited a significant rise, even though PVR did not increase. Some investigators have suggested that the increase in right-sided pressures after administration of verapamil reflects its negative inotropic effect on LV myocardium. However, we do not know if the small, but statistically significant increases in LV filling and right-sided pressures in our patients are due to this effect.

Numerous studies have shown that afterload reducing agents improve LV wall motion abnormalities. In contrast, a recent report indicates that verapamil selectively depresses contractile function in ischemic myocardium of experimental animals. We found no evidence that verapamil exacerbates LV asynergy in most patients with CAD — 70% of all asynergic segments improved or remained the same after the drug was administered, and only 30% deteriorated further. Verapamil's action on LV asynergy is therefore more similar to other afterload-reducing agents than to myocardial depressants.

Verapamil appears to be a very safe agent for use in patients with CAD. It does not depress myocardial performance, and there is no evidence that it frequently worsens LV asynergy. Unlike β blockers, it can be safely given to patients with obstructive airways disease. The effect of verapamil on myocardial metabolism and angina threshold in patients with ischemic heart disease remains to be determined.

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