data, it appears that if verapamil is administered three times daily, increasing the dose of verapamil to more than 360 mg/day is rarely indicated.

Thus, verapamil is highly effective in the treatment of stable effort-related angina, and is well tolerated when the daily dose is 360 mg/day or less.

Acknowledgment

We are indebted to Clifford Rousseve for his technical assistance and Debra Meza for her secretarial assistance. We are also grateful for the statistical consultation of Dr. Perri Stinson.

References


The 24-hour Ambulatory Blood Pressure Profile with Verapamil

BRIAN A. GOULD, M.B., STEWART MANN, M.A., HASSAN KIESO, M.B.,
V. BALA SUBRAMANIAN, M.D., AND EDWARD B. RAFTERY, B.SC., M.D.

SUMMARY The blood pressure response in hypertensive subjects to chronic treatment with verapamil, a calcium antagonist (or, more precisely, a slow-channel inhibitor), was studied using the Oxford system for continuous monitoring of intraarterial blood pressure. Sixteen patients underwent continuous monitoring over a 48-hour period before and after at least 6 weeks of therapy (dose range 120–160 mg three times daily). Each monitoring period included physiologic tests designed to show the effects of different types of exercise. Verapamil produces a consistent reduction of blood pressure over 24 hours, but particularly during the day. Heart rate was similarly reduced. There was no evidence of postural hypotension, and the absolute responses to dynamic and isometric exercise were reduced. The degree of reduction of the blood pressure was consistent, suggesting that slow-channel inhibitors may be appropriate for antihypertensive therapy.

THE ONLY CONSISTENT hemodynamic difference between hypertensive and normotensive persons is an increase in the peripheral resistance. This presumably arises because of arteriolar vasoconstriction, and although the mechanism of this effect is not known, it would seem logical to counteract the vasoconstriction by using drugs that produce direct vasodilatation. Verapamil is a slow calcium-channel blocking drug, derived from papaverine. It has been widely used to treat arrhythmias and has an antiangiinal effect in high dosages. It is a potent peripheral vasodilator, acting directly on arteriolar smooth muscle, and reduces arterial blood pressure after i.v. injection. There have been a number of reports suggesting that it is also effective given orally. We performed a controlled study to monitor the reduction of the blood pressure over 24 hours achieved with verapamil in patients with essential hypertension using the Oxford system for continuous recording of intraarterial blood pressure. Recent studies in our department demonstrated that the administration of placebo alone has no demonstrable effect on the intraarterial blood pressure. As a result of these data and the invasive nature of the technique, a double-blind placebo crossover trial was not considered justified.
Materials and Methods

Twenty patients with essential hypertension (six females and 14 males), ages 31–64 years, were recruited from the Harrow Hypertension Clinic. In all patients, secondary causes of hypertension were excluded by routine screening tests. Only those patients whose mean clinic pressure from three outpatient readings exceeded 160 mm Hg systolic or 95 mm Hg diastolic were selected. The mean length of diagnosed hypertension of the group was 2.25 years (range 0–10 years). None of the group had malignant hypertension and none had exudates or hemorrhages in the fundi. Seven patients did have arteriovenous nipping. There was no evidence of renal impairment and all blood ureas were less than 6.5 mmol/l. None of the patients had cardiac decompensation or other significant pathology. Seven patients were taking antihypertensive therapy when first seen in the clinic. Four were taking thiazide diuretics, one diuretics and \( \beta \)-adrenergic receptor blockers and one \( \beta \)-adrenergic receptor blockers as sole therapy. This antihypertensive therapy had failed to lower the blood pressure adequately in these patients. All patients had a 4-week period on no therapy before entering the study. During the trial, the patients took no other medications. The study was approved by the Hospital Ethical Committee.

The technique has been described.\(^{18,19}\) Briefly, patients attended hospital for percutaneous insertion of an intraarterial cannula into the brachial artery of the nondominant arm. The blood pressure signal was recorded with a transducer unit\(^{20}\) and was recorded with the ECG signal from chest electrodes on a Medilog Mark 1 miniaturized tape recorder (Oxford Medical Systems).

After the cannula had been inserted, each patient underwent a planned program of exercise. At the commencement of this period, each rested supine on a tilt table for 20 minutes. The table was then tilted rapidly to 60° head-up position (after warning) which was maintained for 5 minutes. The maximal hand grip was then recorded using a dynamometer and a 2-minute handgrip at 50% of maximal was then recorded. Any tendency to the Valsalva maneuver was avoided by requesting the patient to count aloud.

After a rest period, each patient rode a bicycle ergometer with loads increasing from 250, 400, 700 to 1000 kpm at 3-minute intervals; exercise was stopped earlier at the patient's request. After finishing the exercise, each was returned to the supine position for 5 minutes of rest. Patients were then allowed to go about their normal daily routine, only attending the hospital for equipment and calibration checks at 12-hour intervals. The recordings were continued for 36–48 hours, after which the cannulas were withdrawn.

One week later, verapamil, 120 mg three times daily, was prescribed for all patients, who were then seen regularly in the outpatient clinic. This dose reduced the blood pressure as measured in the clinic, and was adequate in all but three, in whom the dose was increased to 160 mg three times daily. After at least 6 weeks (mean 12 weeks) at a constant dosage, the intraarterial monitoring was repeated exactly as in the pretreatment study.

The tape recordings were initially replayed and written out in full using a pen recorder. Mean hourly values for heart rate and blood pressure were computed using a hybrid computer\(^{21}\) and the data were pooled. Mean values for each hour of a 24-hour cycle before and after treatment were calculated and the difference was assessed statistically using a two-tailed paired \( t \) test.

The supine rest, tilt, isometric and bicycle exercise data were computed using a digitizing program on the hybrid computer. In the last 5 minutes of supine rest, a mean pressure over 30 beats during each minute was computed. During the tilt, mean pressures over consecutive 10-beat periods were computed for the first 200 beats. At the peak of isometric exercise the mean pressure over 20 beats was digitized. During exercise, the pressures over 30 beats at the end of each 1-minute period were digitized and the mean was used for further analysis. The differences before and after therapy were again assessed by the two-tailed paired \( t \) test. If paired data were missing due to the different exercise times in the same patients, the data were omitted.

Results

Twenty patients entered the study; 16 of them completed the trial. Three were withdrawn because of side effects and one patient was unwilling to be restudied.

Clinic Pressures

Mean supine clinic pressures in the 16 patients after 5 minutes of rest before treatment was 182/105 mm Hg and fell to 149/82 mm Hg after therapy (table 1). Mean standing blood pressure before treatment was 183/110 mm Hg and fell to 145/86 mm Hg (table 1). All reductions were significant (\( p < 0.001 \)). In all but four patients, blood pressure was reduced to lower

<table>
<thead>
<tr>
<th>Table 1. Clinic and Intraarterial Blood Pressures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before therapy</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Clinic BP, supine</td>
</tr>
<tr>
<td>Clinic BP, standing</td>
</tr>
<tr>
<td>Intraarterial BP, mean daytime (noon to 6 pm)</td>
</tr>
<tr>
<td>Supine rest (minutes)</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

\( p < 0.001 \) before vs after treatment for all measurements, systolic and diastolic.

Abbreviation: BP = blood pressure.
than 160/95 mm Hg, and even those four patients showed significant reductions.

Ambulatory Pressures

The mean daytime intraarterial ambulatory blood pressure (calculated by averaging the hourly mean blood pressures between noon and 6 p.m.) was reduced from 180/95 mm Hg before therapy to 158/79 mm Hg after therapy (table 1).

The pretreatment 24-hour curves show a circadian pattern similar to that previously reported. The highest blood pressure levels occurred between 8:00 a.m. and 1:00 p.m. Blood pressure then gradually decreased until 2 a.m., and then increased until 7 a.m., when the rate of rise rapidly increased. Verapamil therapy resulted in a reduction of the blood pressure throughout the day and most of the night, with preservation of the overall shape of the circadian curves.

There was a statistically significant reduction in mean systolic and diastolic blood pressure during 12 of the 24 hours (p < 0.01). Loss of significance occurred mainly during the night. The hourly mean heart rate was also significantly reduced in 19 of the 24 hours (fig. 1).

At the end of 20 minutes of supine rest, the mean intrarterial pressure of the group was reduced from 173/88 mm Hg (table 1) before treatment to 146/71 mm Hg after treatment. All reductions were significant (p < 0.001) and were repeatable over the 5 minutes studied. The mean of the 10 beats immediately before tilting and a 10-beat mean for the subsequent 200 beats are shown in figure 2. After therapy, all of the 10-beat means were significantly reduced, but there was no evidence of postural hypotension.

After 2 minutes of sustained handgrip exercise, the untreated blood pressure peaked at 222/127 mm Hg. After therapy, this peak was reduced to 195/100 mm Hg (table 2). This reduction in the blood pressure was statistically significant (p < 0.001). Before bicycle ergometry, the pretreatment resting blood pressure was 181/93 mm Hg. During the tenth minute of exercise, when half the patients were still exercising, it rose to 240/113 mm Hg (table 3). After therapy, the blood pressure increased from 159/80 mm Hg before exercise to 214/98 mm Hg during the tenth minute of exercise. The reductions in exercise blood pressures during the tenth minute after therapy were significant (p < 0.001 systolic and p < 0.05 diastolic). The trend plots (fig. 3) of the bicycle exercise test showed a consistent and significant reduction in systolic and diastolic pressures (p < 0.05 to < 0.001). The heart rate was also reduced by 10–12 beats/min after therapy (p < 0.05 to < 0.001). The overall levels of the blood pressure during isometric and bicycle exercise were significantly reduced by therapy, but the percent increase in pressure was unaffected.

Side Effects

Four patients reported mild constipation, which did not require withdrawal of therapy. One patient complained of epigastric pains, which subsided after with-
drawal of therapy. One patient reported a burning sensation in the gums and experienced severe facial pains, but the symptoms subsided on withdrawal of therapy. In one patient with epigastric pains and burning sensation in the gums, verapamil was restarted after an interval of 8 weeks. Symptoms returned after 3 days and therapy was promptly terminated.

### Table 2. Reductions of Intraarterial Blood Pressure at Peak of Isometric Exercise

<table>
<thead>
<tr>
<th>Pt</th>
<th>Before therapy</th>
<th>After therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>201/111</td>
<td>179/99</td>
</tr>
<tr>
<td>2</td>
<td>230/148</td>
<td>214/115</td>
</tr>
<tr>
<td>3</td>
<td>216/128</td>
<td>188/95</td>
</tr>
<tr>
<td>4</td>
<td>222/100</td>
<td>195/93</td>
</tr>
<tr>
<td>5</td>
<td>213/126</td>
<td>178/96</td>
</tr>
<tr>
<td>6</td>
<td>205/115</td>
<td>209/118</td>
</tr>
<tr>
<td>7</td>
<td>250/120</td>
<td>230/99</td>
</tr>
<tr>
<td>8</td>
<td>255/149</td>
<td>232/128</td>
</tr>
<tr>
<td>9</td>
<td>162/96</td>
<td>151/93</td>
</tr>
<tr>
<td>10</td>
<td>204/151</td>
<td>174/95</td>
</tr>
<tr>
<td>11</td>
<td>218/117</td>
<td>218/101</td>
</tr>
<tr>
<td>12</td>
<td>255/153</td>
<td>198/90</td>
</tr>
<tr>
<td>13</td>
<td>226/128</td>
<td>183/95</td>
</tr>
<tr>
<td>14</td>
<td>246/129</td>
<td>174/84</td>
</tr>
<tr>
<td>15</td>
<td>190/107</td>
<td>175/93</td>
</tr>
<tr>
<td>16</td>
<td>255/149</td>
<td>218/102</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>222/127 ± 27/18</td>
<td>195/100 ± 23/11</td>
</tr>
<tr>
<td>$t$</td>
<td>5.562</td>
<td>5.650</td>
</tr>
<tr>
<td>$p$</td>
<td>$&lt; 0.001$</td>
<td>$&lt; 0.001$</td>
</tr>
</tbody>
</table>

### Table 3. Bicycle Exercise, Mean Blood Pressures Pre-exercise and Individual Blood Pressures at Tenth Minute of Exercise

<table>
<thead>
<tr>
<th>Mean BP before therapy</th>
<th>Mean BP after therapy</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before bicycle exercise</td>
<td>181/93 ± 25/14</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Individual BP at 10th minute of exercise</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pt</th>
<th>Before therapy</th>
<th>After therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>209/97</td>
<td>187/96</td>
</tr>
<tr>
<td>3</td>
<td>241/111</td>
<td>212/93</td>
</tr>
<tr>
<td>4</td>
<td>252/95</td>
<td>223/82</td>
</tr>
<tr>
<td>5</td>
<td>234/114</td>
<td>219/111</td>
</tr>
<tr>
<td>6</td>
<td>247/134</td>
<td>224/118</td>
</tr>
<tr>
<td>7</td>
<td>255/126</td>
<td>215/83</td>
</tr>
<tr>
<td>9</td>
<td>210/113</td>
<td>203/114</td>
</tr>
<tr>
<td>15</td>
<td>254/113</td>
<td>223/85</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>240/113 ± 19/13</td>
<td>214/98 ± 13/15</td>
</tr>
<tr>
<td>$t$</td>
<td>6.795</td>
<td>2.863</td>
</tr>
<tr>
<td>$p$</td>
<td>$&lt; 0.001$</td>
<td>$&lt; 0.05$</td>
</tr>
</tbody>
</table>

**Discussion**

Most of the interest in slow-channel inhibitors is focused on their action in alleviating angina and controlling arrhythmias. Published data on the antihypertensive effect of verapamil is comparatively scarce; earlier papers focused on the i.v. treatment of hypertensive patients, with a few reporting its action in chronic oral dosage. Lewis et al.14 in a double-blind trial, reported a substantial antihypertensive effect of oral verapamil, whereas Pederson not noted only a modest action of the drug in an open trial involving only five hypertensive patients. Leonetti et al.15 in a recent single-blind trial, confirmed the findings of Lewis et al.14

Our trial was open, as recent data from a double-blind placebo crossover trial showed that ambulatory intraarterial blood pressures were not subject to a placebo response, while indirect clinic pressures were lowered significantly.17 We concluded that a placebo control is not required during clinical trials involving intraarterial blood pressure monitoring.

Verapamil caused a consistent and substantial reduction of blood pressure equivalent to, if not better...
than, that in similar studies we have performed assessing β-adrenergic receptor blockers,18, 22-24 Verapamil lowers the blood pressure by producing vasodilation in the resistance vessels.5, 8 Despite its negative inotropic activity, a reduction of myocardial contractility is unlikely to contribute to the hypotensive effect. On the contrary, Ferlinz et al.9 demonstrated an increase in cardiac output and increased contractility as measured by the ejection fraction and velocity of circumferential fiber shortening. The increased cardiac performance may result from the reduction in afterload produced by the fall in peripheral resistance. Similar findings have been reported with another slow-channel inhibitor, nifedipine.26

Although other vasodilators cause fluid retention28 when used alone, this does not seem to be a problem with verapamil.23 Our results indicate that in many instances verapamil could be used as the sole therapy for hypertension, although a diuretic (which has been shown to potentiate the effect29) may be necessary in some cases.

The blood pressure reduction was especially notable during the early morning (1:00–10:00 a.m.), confirmed when the curves were normalized to the time of awakening (fig. 4). Similar normalization in studies involving β-adrenergic receptor blockers18, 22-24 have shown little effect at this time, although other studies have shown smoother control.28 The conjectured association of a peak incidence of stroke,29 sudden death30 and myocardial infarction31 at this time leads us to believe that a hypotensive effect at this period of the day is important.

With this degree of blood pressure reduction, reflex tachycardia might have been expected, but we demonstrated a consistent reduction of the heart rate. Reports conflict in suggesting no change,9, 10 a decrease22, 23 and even an increase in heart rate after treatment.34, 35 The varying response of the heart rate in different studies may depend on the interaction between direct and reflex effects.

Verapamil significantly reduced the blood pressure response to various exercise procedures. During each of the last 5 minutes of supine rest the blood pressure was significantly reduced (table 1). There was no postural hypotension on tilting, which would suggest that the hypotensive action of the drug is purely due to peripheral vasodilatation, with no α-adrenoceptor blocking activity.

Isometric exercise is associated with a marked increase in the blood pressure. The physiologic mechanism of this rise is not fully understood. Donald et al.36 reported data that suggest that the rise in blood pressure occurs mainly as a result of an increase in heart rate, with little change in the peripheral resistance. Taylor37 argued that the increase in blood pressure is due mainly to an increase in peripheral resistance. Whatever the underlying mechanism, antihypertensive agents do not seem to have a significant effect on this response.38, 39 Verapamil, however, caused a significant reduction in the absolute blood pressure at the peak of isometric exercise, but the percent of change was unaffected. Isometric exercise is a component of various activities of daily living and a modified blood pressure response may be beneficial by lowering the peaks of pressure that occur throughout the day.

During bicycle exercise, similar studies involving β-adrenergic receptor blocking agents have demonstrated a significant reduction in the blood pressure during the lower grades of work but not during the highest grades.29, 34 These findings may be the result of either fewer patients sustaining the higher work loads or the effect of isometric exercise at high work loads. In contrast, verapamil resulted in a smooth reduction in the blood pressure throughout the exercise and postexercise period, although the percentage increase in pressure was unaffected. Hemodynamic studies40-42 suggest that most of the rise in blood pressure during dynamic exercise results from an increase in peripheral resistance, although this view has been challenged.39 Accepting the increase in pressure as the result of increased peripheral resistance, the vasodilatory mode of action of verapamil might explain its better performance in reducing exercise blood pressures compared with β-adrenergic receptor blockers.

In conclusion, we have found a substantial and consistent antihypertensive effect of verapamil, effective over most of the 24 hours when the drug was administered three times daily in a dosage of 360–480 mg/day. The heart rate was also modestly reduced during most of the 24 hours. Verapamil also lowered the blood pressure during isometric and dynamic exercise.

![Graph](http://circ.ahajournals.org/)

**Figure 4.** Mean hourly heart rate and blood pressure corrected to the time of waking before (●) and after (○) verapamil. Vertical lines between curves indicate p < 0.05 (●●●●), p < 0.01 (●●●●), or p < 0.001 (●●●●).
testing. The patients had no evidence of postural hypotension. We believe that these findings, with the results of others, may herald the use of a new class of antihypertensive agent, the slow-channel inhibitors, into the management of hypertension.

Acknowledgment

We thank P.M.M. Cashman for assistance with computer programming, T. Vadgama and S. Dashwood for technical assistance and J. Loveday for secretarial help.

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