Hemodynamic Consequences of Combined Beta-adrenergic and Slow Calcium Channel Blockade in Man

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SUMMARY The administration of verapamil to patients receiving β-adrenergic blocking drugs is reported to produce adverse circulatory reactions, but a systematic investigation of this potential drug interaction has not been performed in man. We administered 40-, 80- and 120-mg doses of verapamil orally to 15 patients with angina pectoris who were receiving high doses of propranolol or metoprolol. Verapamil produced dose-dependent decreases in cardiac performance with 120 mg, cardiac index decreased by 0.381/min/m², stroke volume index decreased by 2.8 ml/beat/m² and heart rate decreased by 6 beats/min, associated with increases in pulmonary capillary wedge (2.2 mm Hg) and mean right atrial pressures (1.7 mm Hg) (all p < 0.01); two patients had marked, but asymptomatic, hypotensive reactions. In contrast, repeat administration of 120-mg doses of verapamil 24–30 hours after withdrawal of β blockade produced no significant cardiodepressant effects despite significantly higher plasma levels of verapamil than during propranolol therapy (383.1 vs 205.1 ng/ml, p < 0.01). In conclusion, verapamil produces significant negative inotropic and chronotropic effects in patients treated with β-adrenergic antagonists; combination therapy should therefore be used with caution in patients with angina pectoris.

DRUGS that block slow-channel activity in cardiac and vascular smooth muscle are being used in an increasing number of cardiovascular disorders. These drugs, such as verapamil, nifedipine and diltiazem, are also known as calcium antagonists because of the dominant role of the calcium ion in slow-channel activity. The calcium antagonists are potentially useful for treating patients with supraventricular tachyarrhythmias, exertional and vasospastic angina pectoris and idiopathic hypertrophic subaortic stenosis, particularly after conventional therapy with β-blocking drugs has failed. Because of their negative inotropic and chronotropic effects and their inhibitory actions on atrioventricular conduction, these agents were initially believed to be β-adrenergic antagonists, but experimental studies have clearly distinguished their mode of action from compounds that block β-adrenergic receptors.

Combined therapy with calcium antagonists and β-blocking drugs has been avoided because of fears that such treatment would produce additive and potentially detrimental circulatory responses. This has been particularly true of verapamil because its administration to animals receiving propranolol synergistically decreased myocardial contractility and prolonged atrioventricular conduction time. These initial concerns were supported by clinical reports of hypotension and ventricular asystole when verapamil was administered to patients receiving propranolol and other β-adrenergic antagonists. Although these events occurred exclusively in patients who received i.v. verapamil for treatment of supraventricular tachyarrhythmias, the Food and Drug Administration advised against the concomitant use of β-receptor antagonists and verapamil (both oral and i.v.) for all investigational indications and suggested that β-blockers be withheld for 48 hours before verapamil therapy is instituted.

However, in patients with coronary artery disease in normal sinus rhythm, verapamil produces minimal overall negative inotropic effects. Studies have suggested that the ability of the drug to dilate peripheral vessels reduces ventricular afterload and hence serves to counteract the negative effects on myocardial contractility. When these vasodilator properties predominate, verapamil may actually improve cardiac performance and increase cardiac output and ejection phase indexes. Similarly, nifedipine has been used to treat acute heart failure and reduce the regurgitant fraction in patients with severe valvular insufficiency. As a result, the prohibition concerning combined slow-channel and β-receptor blockade has been questioned, especially because recent studies have suggested that such therapy may be superior to the beneficial effects of either agent administered alone.

Because the hemodynamic effects of oral verapamil have not been investigated and a systematic evaluation of the potential for adverse reactions during concomitant therapy with β-adrenergic antagonists has not been performed in man, we evaluated the hemodynamic effects of oral verapamil in different doses in patients treated with high doses of β-blocking agents. We reevaluated these effects 24 hours after β blockers were withdrawn.

Methods

Patient Population

We evaluated 15 patients (seven men and eight women) with severe angina pectoris refractory to opti-
mal conventional therapy with nitrates and β-blocking drugs. The patients were 33–87 years old (mean 56 years). Thirteen patients had severe multivessel coronary artery disease, one of whom had idiopathic hypertrophic cardiomyopathy; two patients had an idiopathic hypertrophic cardiomyopathy and normal coronary arteries. The diagnosis of coronary artery disease was established by cardiac catheterization in all cases. All patients with hypertrophic cardiomyopathy had a subaortic gradient greater than 30 mm Hg with provocation, but none had a gradient at rest. The left ventricular ejection fraction, determined by contrast or radionuclide ventriculography within 1 week before the study, ranged from 35–78% (mean 52%). Seven patients had had a myocardial infarction, but not in the previous 3 weeks. Four patients had undergone coronary artery bypass surgery; coronary cineangio-arteriography demonstrated closed grafts in all. Five patients had a history of systemic hypertension, three had diabetes mellitus and one patient had systemic lupus erythematosus. All patients were in normal sinus rhythm; two patients had first-degree atrioventricular block, one patient had right bundle branch block and one had left bundle branch block. The protocol was approved by the Human Studies Committee of the Mount Sinai Medical Center, and all patients gave written, informed consent.

All patients had been treated with high doses of β-blocking drugs for 1 week to 7 years (mean 23 months) before entry into the study; this consisted of oral propranolol (160–1280 mg/day, mean 502 mg/day) in 13 patients and metoprolol (400 mg/day) in two patients; propranolol and metoprolol were both administered in four divided doses in quantities that had remained unchanged for at least 5 days. Four patients who had resting angina pectoris requiring nitrates also received a continuous infusion of i.v. nitroglycerin (33–100 μg/min), the dose of which remained unchanged throughout the study; no other patient required or received nitrates within 24 hours before or during the study. Two patients had recently received diuretic agents (one furosemide and one spironolactone); both drugs were continued unchanged but were not administered simultaneously with verapamil, so as to permit study of independent drug effects. Two patients had received methyldopa within the past week but not within 2 days; no patient was treated with digitalis or antiarrhythmic therapy. No other cardioactive medications were administered before or during the trial.

Hemodynamic Measurements

All medications except propranolol and metoprolol were withheld on the morning of the study. Right-heart catheterization was performed to measure right atrial, pulmonary arterial and pulmonary capillary wedge pressures in all patients. Thermomilulation cardiac outputs were determined in triplicate by a bedside computer (Instrumentation Laboratories) using iced injectate. Arterial cannulas were inserted into the radial artery of all patients to measure systemic pressures. All determinations were made with zero reference level at the mid-chest with the patient supine. Heart rates were derived from a continuously recorded single-lead ECG, from which PR and QRS intervals were also evaluated in 10 patients by measurement of five consecutive electrocardiographic complexes.

Drug Administration

The study consisted of 3 days of verapamil administration during intensive hemodynamic evaluation (fig. 1). At the beginning of each day and before each dose of the drug, the following hemodynamic variables were repeatedly determined over a period of 2 hours to ensure stability of the control hemodynamic state before the administration of verapamil: cardiac output, heart rate and mean systemic arterial, mean pulmonary arterial, mean pulmonary capillary wedge and mean right atrial pressures. On day 1, each patient received a test dose of 2 mg of i.v. verapamil as a precaution because of the potential for adverse hemodynamic consequences. The test dose was followed by a 40-mg oral dose 1–2 hours later and an 80-mg oral dose 4 hours after the administration of 40 mg. On days 2 and 3, each patient received two 120-mg doses of verapamil 6 hours apart. During days 1 and 2, propranolol or metoprolol were administered in their usual doses every 6 hours, but each dose of verapamil coincided with or followed within 1–2 hours a dose of propranolol or metoprolol. Therapy with β-blocking drugs was abruptly discontinued after administration of the dose that coincided with the first 120-mg dose of verapamil, on day 2. The second, third and fourth 120-mg doses of verapamil were therefore administered 6 hours, 21–25 hours and 27–31 hours

Figure 1. Schematic representation of protocol design. Increasing doses of verapamil were administered under similar hemodynamic conditions during treatment with β blockers (cross-hatched area); black rectangles indicate administration of propranolol and metoprolol. All hemodynamic variables (collectively represented here by cardiac index, CI) were determined every 30 minutes. Doses of 120 mg of verapamil were readministered 6, 21–25 and 27–31 hours after withdrawal of β blockade. Each interval designated on the abscissa represents 1 hour.
Table 1. Hemodynamic Responses to Verapamil During and After Withdrawal of β Blockade

<table>
<thead>
<tr>
<th></th>
<th>40 mg (n = 12)</th>
<th>80 mg (n = 12)</th>
<th>120 mg (n = 15)</th>
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<tr>
<td></td>
<td>C</td>
<td>V</td>
<td>C</td>
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<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.32 ± 0.11</td>
<td>2.12 ± 0.10</td>
<td>2.34 ± 0.12</td>
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<td></td>
<td>2.44 ± 0.07</td>
<td>2.06 ± 0.07</td>
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<tr>
<td>Stroke volume index (ml/beat/m²)</td>
<td>38.4 ± 2.5</td>
<td>36.8 ± 1.9</td>
<td>39.2 ± 1.7</td>
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<td></td>
<td>37.7 ± 2.2</td>
<td>36.5 ± 2.2</td>
<td>39.2 ± 1.7</td>
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<td>Heart rate (beats/min)</td>
<td>66 ± 3</td>
<td>59 ± 3</td>
<td>62 ± 3</td>
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<td></td>
<td>63 ± 3</td>
<td>63 ± 3</td>
<td>63 ± 3</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>84.2 ± 5.5</td>
<td>75.2 ± 5.5</td>
<td>84.3 ± 6.2</td>
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<td></td>
<td>83.0 ± 4.6</td>
<td>69.8 ± 2.8</td>
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<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>9.6 ± 1.6</td>
<td>9.8 ± 1.7</td>
<td>9.2 ± 1.6</td>
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<td></td>
<td>9.0 ± 1.5</td>
<td>11.2 ± 1.5</td>
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<tr>
<td>Mean pulmonary artery pressure (mm Hg)</td>
<td>16.3 ± 1.9</td>
<td>16.0 ± 1.8</td>
<td>16.2 ± 1.8</td>
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<tr>
<td></td>
<td>17.1 ± 2.2</td>
<td>17.2 ± 1.7</td>
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<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>3.2 ± 0.8</td>
<td>3.7 ± 1.0</td>
<td>3.1 ± 0.8</td>
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<tr>
<td></td>
<td>4.3 ± 0.7</td>
<td>6.0 ± 1.0</td>
<td></td>
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<tr>
<td>Systemic vascular resistance (dyn-sec/cm²)</td>
<td>1613 ± 93</td>
<td>1557 ± 117</td>
<td>1616 ± 120</td>
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<td></td>
<td>1511 ± 116</td>
<td>1431 ± 76</td>
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*p < 0.001 vs control.
†p < 0.01 vs control.
‡p < 0.05 vs control.

Abbreviations: C = control; V = verapamil.

after withdrawal of β blockade. Hemodynamic determinations were performed every 5 minutes for 30 minutes after an i.v. dose of verapamil and every 30 minutes for 4-6 hours after each oral dose of the drug. Changes in the PR and QRS intervals were evaluated before and 90 minutes after each oral dose. The patients were fed liquid diets during the period of hemodynamic measurements. The first day of the protocol was omitted in the last three patients who entered the study; one patient failed to complete day 3 for technical reasons.

Plasma Drug Levels

Blood specimens for plasma levels of propranolol (13 patients) and verapamil (15 patients) were drawn 90 minutes after each oral dose of verapamil. Propranolol levels were determined by high-pressure liquid chromatography (Bio-Science Laboratories), and verapamil levels were determined by gas-liquid chromatography.20, 21

Data Analysis

Mean systemic and pulmonary arterial pressures were determined by electronic filtration. Derived hemodynamic variables were determined as follows:

CI = CO/body surface area (l/min/m²)
SVI = CI/HR (ml/beat/m²)
SVR = 80 x (MAP - MRAP)/CO (dyn-sec-cm⁻²)

where CI = cardiac index, CO = cardiac output, SVI = stroke volume index, HR = heart rate, MAP = mean arterial pressure, and MRAP = mean right atrial pressure. The hemodynamic variables during the peak effect of verapamil (1½-2 hours after oral administration) in each patient were compared with the control values obtained before the administration of each dose of the drug. The hypotheses that verapamil-induced changes in each hemodynamic variable were dose-related and differed during and after withdrawal of β blockade were evaluated by a repeated-measures, two-way analysis of variance using specified linear contrasts.22 The same statistical procedures were applied to the comparison of the control hemodynamic values recorded before each dose of verapamil and to the analysis of plasma levels of verapamil and propranolol drawn after each dose of verapamil. The latter analysis was limited to the 11 patients who completed all 3 days of the study. Duncan’s multiple range test was used to differentiate mean responses. The hemodynamic effects of each dose of verapamil were compared with their respective control values by paired t test. Group data were expressed as the mean ± SEM.

Results

Hemodynamic Effects

The hemodynamic responses to the administration of oral verapamil during and after withdrawal of β blockade are summarized in Table 1 and Figures 2 and 3. Hemodynamic variables during each of the seven control periods before the administration of each dose of the drug were not significantly different (p > 0.4). There were no overall effects from the administration of the test dose of 2 mg of i.v. verapamil.

With 40- and 80-mg doses of verapamil during treatment with propranolol and metoprolol, mean arterial pressure decreased (9.0 and 11.5 mm Hg, respectively, both p < 0.01) due to a decrease in cardiac output.
index (0.20 and 0.26 l/min/m², respectively, both p < 0.05), without significant changes in systemic vascular resistance. The decrease in cardiac index was associated with a decrease in heart rate (4 and 5 beats/min, respectively, both p < 0.05), without significant changes in stroke volume index. Mean pulmonary artery, mean pulmonary capillary wedge and mean right atrial pressures did not change significantly. With the first 120-mg dose of verapamil during treatment with β blockers, mean arterial pressure declined substantially (13.2 mm Hg, p < 0.01) secondary to a significant decrease in cardiac index (0.38 l/min/m², p < 0.001) without changes in systemic vascular resistance. The decrease in cardiac index was accompanied by both a decrease in heart rate (6 beats/min, p < 0.01) and in stroke volume index (2.8 ml/beat/m², p < 0.01). Pulmonary capillary wedge and mean right atrial pressures increased significantly (2.2 mm Hg, p < 0.001 and 1.7 mm Hg, p < 0.01, respectively), without changes in mean pulmonary arterial pressure. The magnitude of the changes in cardiac index, heart rate, stroke volume index and in mean arterial, pulmonary capillary wedge and mean right atrial pressures during treatment with β-adrenergic antagonists became progressively more marked as the dose of verapamil was increased (40, 80 and 120 mg) (linearly significant at p < 0.01). The hemodynamic responses to the second 120-mg dose of verapamil were quantitatively and qualitatively similar to those after the first administration of this dose.

The duration of these hemodynamic effects was brief. Even after the administration of 120-mg doses of verapamil, decreases in cardiac index and in heart rate persisted for only 2–3 hours, returning to control values within 4 hours after oral administration; in only three patients did the hemodynamic responses persist longer. The hemodynamic responses to verapamil were not related to history of myocardial infarction, the pretreatment hemodynamic state or left ventricular ejection fraction, the dose of propranolol before verapamil or concomitant therapy with i.v. nitroglycerin. Responses in the three patients with idiopathic

<table>
<thead>
<tr>
<th>Table 1. (Continued)</th>
<th>After withdrawal of β blockade</th>
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<tr>
<td>(6 hrs)</td>
<td>(21–25 hrs)</td>
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<tr>
<td>120 mg</td>
<td>120 mg</td>
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<tr>
<td>(n = 15)</td>
<td>(n = 14)</td>
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<tr>
<td>C</td>
<td>V</td>
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<tr>
<td>2.42</td>
<td>2.09*</td>
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<td>±0.06</td>
<td>±0.08</td>
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<tr>
<td>40.8</td>
<td>37.6†</td>
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<tr>
<td>±1.8</td>
<td>±1.5</td>
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<td>79.1</td>
<td>68.9†</td>
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<td>±9.6</td>
<td>±12.4*</td>
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<td>±18.0</td>
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<tr>
<td>±4.9</td>
<td>±6.3†</td>
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<tr>
<td>1422</td>
<td>1392</td>
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<tr>
<td>±81</td>
<td>±83</td>
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Figure 2. Changes in cardiac index (CI), heart rate (HR), mean arterial pressure (MAP) and systemic vascular resistance (SVR) after 40-mg, 80-mg and 120-mg doses of verapamil during treatment with β blockers and after three additional 120-mg doses of verapamil 6, 21–25 and 27–31 hours after withdrawal of β blockade. *p < 0.001; †p < 0.01; ‡p < 0.05. Significance of differences between the first 120-mg dose of verapamil (on β blockers) and the fourth administration of this dose (off β blockers) are designated by the bars above the graphs.
hypertrophic cardiomyopathy did not differ from those in patients with coronary artery disease; similarly, the effects in the two patients receiving metoprolol were similar to those patients treated with propranolol.

Twenty-four hours after the withdrawal of β blockers, 120-mg doses of verapamil decreased mean arterial pressure (10.2 and 6.9 mm Hg, respectively, both \( p < 0.01 \)) due to a decline in systemic vascular resistance (141 and 158 dyn-sec-cm\(^{-5} \), both \( p < 0.001 \)), without changes in cardiac index. Stroke volume index, heart rate and mean pulmonary arterial, pulmonary capillary wedge and mean right atrial pressures did not change significantly. Despite similar control variables, verapamil therapy produced significantly greater decreases in cardiac index, heart rate and stroke volume index, and greater increases in pulmonary capillary wedge and mean right atrial pressures with the first 120-mg dose (during therapy with propranolol or metoprolol) than during the fourth 120-mg dose (27–31 hours after discontinuation of β blockade) \( p < 0.05 \). The magnitude of the changes in these hemodynamic variables with the first 120-mg dose of verapamil was progressively less marked after repeat administration of the same dose after discontinuation of β blockade (linearly significant at \( p < 0.01 \)).

**Plasma Drug Levels**

The mean ± SEM of plasma levels of propranolol and verapamil 90 minutes after each dose of verapamil are shown in figure 4. The mean plasma levels of propranolol were 390.5, 406.2 and 474.7 ng/ml after 40-, 80- and 120-mg doses of verapamil, respectively (NS). Plasma levels of propranolol decreased linearly and significantly to 297.0, 71.6 and 40.6 ng/ml at 7.5, 22.5–26.5 and 28.5–32.5 hours, respectively, after propranolol withdrawal \( p < 0.001 \). The mean plasma levels of verapamil were 58.3, 98.0 and 205.1 ng/ml after 40-, 80- and 120-mg doses of the drug, respectively, during the coadministration of propranolol; the progressive increase in these values was significant \( p < 0.01 \). Further, plasma levels of verapamil increased linearly and significantly after repeated 120-mg doses (274.7 ng/ml at 7.5 hours, 305.4 ng/ml at 22.5–26.5 hours and 383.1 ng/ml at 28.5–32.5 hours after propranolol withdrawal; \( p < 0.01 \)).

**Electrocardiographic Changes**

The PR interval from the surface ECG did not change significantly after 2-mg i.v. or 40- and 80-mg oral doses of verapamil. The PR interval increased significantly with 120-mg doses of verapamil, from 0.171 ± 0.01 to 0.181 ± 0.01 second during β blockade \( p < 0.01 \), and from 0.168 ± 0.01 to 0.186 ± 0.01 second 27–31 hours after withdrawal of propranolol and metoprolol \( p < 0.01 \). These changes were not significantly different from each other. One patient had two transient episodes of junctional rhythm, ini-

**Figure 3.** Changes in stroke volume and pulmonary capillary wedge pressure with verapamil therapy during and after withdrawal of β blockade. Format as in figure 2. SVI = stroke volume index; PCW = pulmonary capillary wedge pressure.

**Figure 4.** Plasma concentrations of verapamil and propranolol for the 11 patients treated with propranolol who completed all 3 days of the study. Values are mean ± SEM. Hours at the bottom of the graph designate the time when plasma levels were measured after withdrawal of propranolol, where ~24 hrs represents 22.5–26.5 hours and ~30 hrs represents 28.5–32.5 hours.
tially 90 minutes after the first 120-mg dose of verapamil during propranolol therapy and again when the same dose of verapamil was administered 6 hours after discontinuation of propranolol; this did not recur during the administration of the same dose of verapamil 23 and 29 hours after propranolol withdrawal. First-degree atrioventricular block was seen in three patients with 120-mg doses of verapamil with and without concomitant β blockade; two of these patients had this finding before verapamil administration and two additional patients had first-degree atrioventricular block with verapamil only after propranolol was discontinued. No advanced degree of atrioventricular block or significant change in QRS duration was observed.

Clinical Effects

All patients tolerated concomitant therapy with verapamil and β blockers without adverse symptoms. Two patients had marked hypotensive reactions (decreases in mean arterial pressure of 30 and 59 mm Hg) with 120-mg doses of verapamil during β blockade, but remained asymptomatic. No signs or symptoms of heart failure were observed. No patient had angina at rest during the study.

Discussion

In the present study, administration of verapamil to patients receiving β-blocking drugs produced moderate but significant negative inotropic and chronotropic effects. Whereas only decreases in heart rate were observed with 40- and 80-mg doses, 120-mg doses produced decreases in stroke volume and increases in right and left ventricular filling pressures as well. In contrast, administration of 120-mg doses of verapamil 24 hours after withdrawal of β blockade produced no significant declines in heart rate or cardiac performance. No patient experienced adverse clinical effects with short-term combined treatment.

Adverse cardiovascular events during combined slow calcium channel and β-adrenergic blockade have been reported. These events consisted of hypotension and ventricular asystole occurring after i.v. verapamil for the treatment of supraventricular tachyarrhythmias. However, similar events can occur with verapamil in the absence of therapy with β blockers. Thus, the importance of concomitant therapy in these reports is unclear because verapamil was not readministered after the withdrawal of β blockade. Further, the potential for interaction of these two classes of drugs has not been evaluated in patients given verapamil orally or for treatment of nondysrhythmic disorders. Therefore, although an adverse interaction has been demonstrated in animals without heart disease and has been postulated to occur in man, the clinical relevance of these observations has been uncertain.

The present report provides the first controlled evidence that significant adverse hemodynamic effects occur in patients with heart disease receiving therapeutic doses of verapamil and propranolol. Such effects may be observed for many hours after discontinuation of β blockade. Although Krikler et al. advised that verapamil not be administered to patients who had received β blockers within 6 hours, our data indicate that an adverse hemodynamic response to combined therapy continues unchanged after 6 hours but is absent after 24 hours. This is compatible with the prolonged duration of action of propranolol in man. Although some investigators have feared that combined therapy with verapamil and propranolol might result in potentially additive detrimental effects on atrioventricular conduction, the primary mode of interaction in our patients appeared to be hemodynamic rather than electrophysiologic. This finding is consistent with reported adverse clinical events. The mechanisms underlying the hemodynamic responses to combined slow-channel and β-adrenergic blockade are complex. In isolated heart preparations, verapamil exerts potent negative inotropic and chronotropic effects due to its ability to inhibit calcium and sodium transport across cell membranes in cardiac muscle. Beta blockade produces similar hemodynamic effects, possibly due to interference with intracellular calcium transport across the sarcoplasmic reticulum. We might therefore expect additive negative inotropic and chronotropic responses to combined slow-channel and β-adrenergic blockade because both types of drugs inhibit, by different mechanisms, calcium transport to active sites within cardiac muscle cells. Bristow et al. showed that the ability of calcium ions to antagonize the effects of slow-channel blockade in the intact dog heart is dependent on β-adrenergic activity; doses of D600, a verapamil analog, administered in quantities too small to shift calcium-response curves were able to do so in the presence of practolol, a β antagonist. The significance of this interaction is magnified in the intact circulation. In vivo, the direct negative inotropic and chronotropic effects of verapamil are greatly modified by the drug’s peripheral vasodilator properties, which are mediated by its inhibition of slow-channel activity in vascular smooth muscle. The resultant decrease in systemic vascular resistance and blood pressure stimulates reflex β-adrenergic nervous system activity, which serves to increase heart rate and contractility and thereby offset the depressant effects of verapamil on sinoatrial function and myocardial contractile force. The peripheral vascular effects of the drug serve to further oppose the potential for a reduction in cardiac output by decreasing ventricular afterload. The hemodynamic responses to verapamil are therefore the net result of the interplay of several forces: the direct depressant effects of the drug, the magnitude of peripheral vasodilation and the degree of preservation of reflex sympathetic nervous system responses.

In the presence of intact β-adrenergic reflexes, the overall effect of verapamil on myocardial performance can be expected to be small. Because reflex sympathetic forces serve to counter the negative inotropic
and chronotropic effects of the drug, i.v. verapamil produces either no change or increases in cardiac output, heart rate and ejection fraction, despite associated decreases in peak dP/dt and increases in ventricular filling pressures, which indicate a depressant effect on cardiac performance.14, 15, 36-40 However, the minimal negative inotropic effects in these studies might have been due not only to the activation of sympathetic reflexes, but also to the low plasma levels of verapamil usually achieved by i.v. administration,41 because the depressant effects of verapamil are dose-dependent.9, 10, 30, 35, 42 Cardiac output may increase as a result of reflex β-adrenergic stimulation when low doses are given, whereas higher doses may produce no change or decreases in ventricular performance, despite marked concomitant decreases in systemic vascular resistance, as reflex responses are overwhelmed by the direct depressant effects of the drug.42 Our results confirm the importance of the dose of verapamil in determining the magnitude of its negative inotropic and chronotropic effects, but the integrity of β-sympathetic reflexes appeared to be more important. Despite the high plasma levels of verapamil in our patients, we observed no overall decreases in heart rate or cardiac output with verapamil in the absence of β blockade; decreases in cardiac performance were more closely related to plasma levels of propranolol than to circulating levels of verapamil.

In contrast, in patients treated with propranolol and metoprolol, whose reflex β-adrenergic responses were attenuated, the negative inotropic and chronotropic effects of verapamil remained unopposed, so that the hemodynamic responses to the drug resembled those seen in isolated heart preparations. Cardiac index, stroke volume, heart rate and mean arterial pressure decreased and left ventricular filling pressure increased with verapamil during concomitant therapy with propranolol and metoprolol, but did not change with readministration of the drug after withdrawal of β blockade, despite significantly higher plasma levels of verapamil, which would have produced more marked cardiodepressant effects.43 These findings are consistent with previous animal studies, in which pretreatment with propranolol attenuated verapamil-induced increases in heart rate and cardiac output and potentiated decreases in contractile force and blood pressure.9-11

Verapamil failed to reduce systemic vascular resistance in our patients during treatment with β-receptor antagonists, but did so after their withdrawal despite plasma levels of verapamil at both times greater than those needed to produce direct peripheral vasodilator effects.14, 15, 41 These observations are similar to those of Rowe et al.,11 who showed that peripheral resistance failed to decrease significantly when verapamil was administered to dogs pretreated with propranolol, but peripheral vasodilation occurred as expected with the same dose of the drug in the absence of propranolol. Because the peripheral effects of verapamil are not mediated by β receptors,8, 10 these observations cannot be attributed to a direct interaction between these two drugs within peripheral vessels. It is more likely that neurogenically mediated peripheral arterial and venous vasoconstriction is evoked in response to verapamil-induced decreases in cardiac output and blood pressure in the presence of β blockade, and serves to offset the direct peripheral vascular effects of the drug.56 This peripheral vasoconstriction probably contributes to the increases in right- and left-heart filling pressures during combined therapy but not with verapamil alone. Therefore, whereas the circulation is supported in patients treated with verapamil alone by reflex β-adrenergic mechanisms, excessive hypotension during combined therapy is probably prevented by α-adrenergic forces. Indeed, of the three patients in our series who had decreases in systemic vascular resistance during verapamil-propranolol administration, two had recently been treated with methyldopa, an inhibitor of α-sympathetic vasomotor tone; these two patients had the most marked decreases in mean arterial pressure (30 and 59 mm Hg) with combined therapy. Severe hypotension has occurred after verapamil given concomitantly with quinidine,20, 43 which also attenuates α-adrenergic responses.44

The findings of the present study must be interpreted in the context of certain limitations and precautions. Adverse hemodynamic and electrophysiologic responses occurred, but no patient experienced adverse clinical events during combined therapy, for several reasons. The duration of combined therapy in the present study was brief, and adverse clinical effects might have appeared during more prolonged treatment. The negative inotropic and chronotropic effects after single doses of verapamil were usually modest and short-lived; cardiac output decreased more than by 20% of control values in only four patients, and persisted for longer than 3 hours in three. Ventricular function in our patients before therapy was generally well preserved (all had ejection fractions ≥ 35%). Chew et al.46 showed that the negative inotropic effects of verapamil may be more evident and precipitation of heart failure most likely in patients whose ejection fractions are less than 30%. Moreover, most patients with angina pectoris seem to tolerate mild-to-moderate decreases in cardiac output well. Indeed, combined therapy might be particularly useful in such patients because propranolol would attenuate verapamil-induced reflex increases in β-adrenergic activity, which might detract from the drug's antianginal properties.5 In patients with exertional angina pectoris, combined slow-channel and β-adrenergic blockade was therapeutically superior to therapy with either drug alone.18, 19

Our patients were treated with large doses of propranolol, which produced high plasma levels of the drug. Even 24 hours after its withdrawal, plasma levels of propranolol remained within the therapeutic range in many of our patients. Had we reevaluated the effects of verapamil 48 hours after discontinuation of propranolol, when residual levels of the drug would have been even lower, we might have observed increases rather than no change in cardiac output in response to the peripheral vasodilator actions of ver-
apamil. Because we observed no adverse hemodynamic effects with the administration of verapamil to patients with low residual levels of propranolol, these might not occur in patients treated with low doses of propranolol, which would produce plasma levels of the drug comparable to those after the withdrawal period in our study. This hypothesis requires direct confirmation.

Finally, the findings of the present study apply only to combination therapy with verapamil and do not necessarily apply to other calcium antagonists, such as nifedipine and diltiazem. Although nifedipine resembles verapamil in depressing slow-channel activity in cardiac muscle, it has minimal direct depressant effects on atrioventricular conduction in man. and neutralization of cardiac depressant effects by peripheral vasodilation seems to be more nearly complete with nifedipine than with verapamil. Hence, combined therapy with β-adrenergic antagonists might be safer with nifedipine than with verapamil. However, in view of recent reports of adverse hemodynamic effects during nifedipine therapy in patients receiving β blockers, further studies are needed to determine the relative safety of various calcium antagonists during β-receptor blockade.

In conclusion, the present study underscores the need for caution when verapamil is administered to patients treated with β-adrenergic blocking drugs. Combination therapy produces significant decreases in heart rate and blood pressure, while simultaneously depressing cardiac performance; rhythm disturbances may also be observed. These circulatory responses can be avoided by withdrawal of propranolol or metoprolol therapy for 24 hours before verapamil administration. These adverse hemodynamic effects are relatively mild during short-term therapy in patients with good left ventricular function and hence may be well tolerated clinically in most patients. In view of studies indicating that combined β-adrenergic and slow-channel blockade may be superior to existing medical therapies for angina pectoris, such patients need to be carefully selected, and blood pressure, heart rate and clinical status should be monitored closely during treatment. Combination therapy should probably be avoided in patients who have recently received drugs that attenuate α-sympathetic responses, because severe hypotensive reactions may occur.

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