The Antihypertensive Mechanism of Verapamil
Alteration of Glomerular Filtration Rate Regulation

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SUMMARY The renal hemodynamic and renin release responses to verapamil were analyzed to determine if the antihypertensive action of the calcium entry blocker could be due to its renal effects. Hemodynamic and renin release measurements were compared in a control group of nine anesthetized rabbits and in a group of 10 rabbits given verapamil (200 μg/kg i.v. initially, 4 μg/kg/min thereafter), starting 30 minutes before data collection. Measurements were made over a range of controlled renal perfusion pressure from 100 to 40 mm Hg. The renal blood flow at 100 mm Hg of the verapamil-treated group was 18% greater (p<0.02) than that of the control group, while the glomerular filtration rate was 51% greater (p<0.001) than that of the control group. Renal blood flow and glomerular filtration rate autoregulation were highly effective in the control group down to 80 mm Hg, but both variables were poorly regulated in the verapamil-treated group. The filtration fraction of the treated group was 36.9 ± 1.5% versus 28.5 ± 1.6% in the control group (p<0.003) at 100 mm Hg, and the filtration fraction of the treated group remained significantly greater down to 40 mm Hg. Renin release rates of the two groups were similar at the 100 mm Hg pressure level, but the increase in release due to the progressive reduction in perfusion pressure was significantly greater in the treated group than in the control group. At the 80 mm Hg pressure level, the mean release rate for the treated group was more than three times greater (p<0.05) than that of the control group. These findings demonstrate that verapamil is an effective renal vasodilator and that the effect is proportionally greater on the preglomerular than on the postglomerular resistance. This action could be the basis for its antihypertensive efficacy. (Hypertension 11: 639–644, 1988)

KEY WORDS • renal hemodynamics • renin • renal blood flow • vasodilation • filtration fraction • hypertension • rabbit

THE primary effect of calcium entry blockers is to reduce the rate of entry of calcium into the cytoplasm of a wide range of cell types. In vascular smooth muscle this effect results in a decrease in cytosolic calcium concentration and a reduction in contractile activity, leading to vasodilation. A variety of calcium entry blockers have proved to be effective in the treatment of hypertension, and the general vasodilator action is believed by many to be the mechanism of the effect. However, many effective vasodilators do not reduce the steady state level of arterial pressure in hypertensive patients, and several maneuvers that drastically affect total peripheral resistance (e.g., pregnancy, amputation, closing an arteriovenous shunt) do not alter long-term arterial pressure level in hypertensive or normal patients. Furthermore, numerous theoretical, experimental, and clinical analyses have supported the hypothesis that the change in peripheral resistance in hypertension is a secondary alteration in cardiovascular function that is not necessarily directly related to the origins of the hypertension. On the basis of these analyses, we have assumed that the antihypertensive efficacy of the calcium entry blockers is due to some action other than a generalized reduction in total peripheral resistance.

Hypertension is a complex multivariate condition about which few generalizations can be made. However, all would agree that in hypertension an alteration exists in the relationship between renal perfusion pressure and renal excretion of sodium and water; hypertensive patients in daily sodium and water balance excrete these substances at normal rates, while their renal perfusion pressure is greater than normal. The primary importance of this alteration has been demonstrated repeatedly in experiments in which it has been
found that any action that will change the relationship between arterial pressure and renal sodium and water excretion will change the steady state level of arterial pressure (for a review, see References 2 and 3). One of the most effective maneuvers that alters the relationship and leads to hypertension is to increase preglomerular vascular resistance. Initially, when preglomerular resistance is greater than normal, glomerular filtration rate (GFR) or peritubular capillary pressure (or both) will be below normal, resulting in a reduction in the rate of sodium and water excretion. The retention of water and sodium will give rise to a progressive increase in arterial pressure that will continue until the effects of the supranormal arterial pressure overcome the sodium-retaining effects of the elevated preglomerular resistance. The classic model that demonstrates these relationships is the Goldblatt experiment. Placing the clamp on the kidney increases preglomerular vascular resistance and thereby alters the relationship between arterial pressure and sodium and water excretion.

Theoretically, reducing preglomerular resistance is an effective means to reduce steady state arterial pressure, again due to the effect on GFR, postglomerular capillary pressure, and sodium and water excretion. Calcium entry blockers decrease total renal vascular resistance,\textsuperscript{4}–\textsuperscript{7} impair autoregulation of renal blood flow in short-term animal preparations,\textsuperscript{8,9} and increase renal blood flow in hypertensive\textsuperscript{10} and normotensive volunteers.\textsuperscript{11} Whether the decrease in resistance is preglomerular or postglomerular is unknown, since many of the required GFR measurements have not been made. If calcium entry blockers do cause preglomerular vasodilation, this action could account for their antihypertensive effect. Therefore, the goal of this study was to analyze the effects of the calcium entry blocker verapamil on renal hemodynamics to determine if the blocker reduced preglomerular resistance. This first set of experiments was conducted in anesthetized rabbits in which the level of renal perfusion pressure could be set at levels from 100 to 40 mm Hg while measurements of renal blood flow (RBF), GFR, and other variables were made. We also analyzed renin release responses over the range of renal perfusion pressure to determine if the calcium entry blocker stimulated renin release, as has been reported in some investigations.\textsuperscript{12,13}

Materials and Methods

The experiments were performed on New Zealand white rabbits (Magnolia Rabbitry, Magnolia, MS, USA) of either sex weighing between 2.7 and 3.8 kg using techniques described previously.\textsuperscript{14} The animals were held in the laboratory animal facilities for at least 2 weeks before being used. They were fed a standard laboratory diet until 15 hours before operation (Rabbit Chow Complete Blend, Purina Mills, St. Louis, MO, USA). They were anesthetized with sodium pentobarbital, 35 mg/kg i.v., injected through the marginal vein of the ear. The trachea was cannulated, and the animals were artificially ventilated as needed to maintain normal blood gas values. Both carotid arteries were exposed; one was cannulated for measurement of arterial pressure, while the other was tied off to stimulate the baroreceptor reflex and elevate systemic arterial pressure. Both femoral arteries and one femoral vein were cannulated for measurement of arterial pressure below the renal arteries, sampling of arterial blood, and intravenous infusions. The left kidney was exposed through a retroperitoneal flank incision. A portion of the aorta above the left renal artery was isolated gently, and a silicone rubber cuff occluder was placed around the aorta. The left renal artery was also isolated, and a 4-mm-circumference electromagnetic flow probe was placed around the left renal artery. An electromagnetic flow meter (Model FM501, Carolina Medical Electronics, King, NC, USA) was used to measure renal blood flow. Finally, a 23-gauge L-shaped needle was inserted into the renal vein for sampling renal venous blood.

The GFR was calculated from the filtration fraction of iothalamate (sodium [\textsuperscript{125}I]iothalamate, Isotex Diagnostics, Friendswood, TX, USA) and renal plasma flow. The [\textsuperscript{125}I] activities in arterial and venous plasma were determined in 0.2-ml samples. Renal plasma flow was obtained from the hematocrit, and the RBF was obtained from the flow meter.

An index of renin release was determined from the difference in plasma renin activity (PRA) between the renal venous and arterial plasma and the renal plasma flow. PRA measurements were made in 0.5 ml of blood placed into iced sodium EDTA tubes and centrifuged for 10 minutes; 0.2 ml of plasma was used for the assay using the radioimmunoassay procedure of Haber et al.\textsuperscript{15} The renin release index from the left kidney was calculated from the product of the venous minus arterial PRA difference and the renal plasma flow divided by the kidney weight. One unit of renin release was taken to be equal to 1 ng of angiotensin I per milliliter per hour, and the rate of renin release was expressed as units per minute per gram of kidney weight.

Experimental Protocol

All animals were given 3% body weight of saline intravenously over a 15-minute period following completion of operation to obtain a consistent, well-hydrated initial condition. A saline infusion of 0.5 ml/min was maintained for the remainder of the experiment. In addition, 5 to 7 \(\mu\)Ci of [\textsuperscript{125}I]iothalamate was given as an i.v. bolus followed by a continuous infusion of 15 to 20 \(\mu\)Ci over the duration of the experiment.

Thirty to 45 minutes after the completion of the operation, data collection began. Measurements were made at normal renal perfusion pressure and at reduced renal perfusion pressures maintained by the operation of a servocontrol mechanism that adjusted the inflation of the aortic cuff to keep the level of arterial pressure below the constrictor at a desired level.\textsuperscript{16} Renal perfusion pressure was reduced in 10 mm Hg steps down to a minimum level of 40 mm Hg. Data were collected at each pressure level after it had been maintained for 8 to
10 minutes. Blood samples of 1.5 ml were obtained from the femoral artery and renal vein at each level of renal perfusion pressure for measurement of hematocrit, PRA, and \(^{21}\) activity.

Two groups of rabbits were studied. The control group consisted of nine rabbits whose body weights averaged 3.27 ± 0.13 kg. Renin release was measured in eight of these. The verapamil-treated group contained 10 rabbits whose body weights averaged 3.24 ± 0.10 kg. Renin release was measured in eight of these. In this group after completion of operation and infusion of 3% body weight of saline, verapamil 200 \(\mu\)g/kg, was infused over a period of 5 to 10 minutes, after which 4 \(\mu\)g/kg/min was infused at a rate of approximately 0.5 ml/min.

Data Analysis

Group means and standard errors of the mean are presented in the text and in some of the figures. Statistical comparisons of all data at specific levels of renal perfusion pressure in the two groups were made using Student's t test for unpaired data. Because we were testing for directional changes in the variables, the tests were one-sided. A probability value of 5% or less was considered indicative of a significant effect. The relationships between renal arterial pressure and the measured variables, all of which are presented in Table 1 and in some of the figures. Statistical comparisons of the slopes of the ellipsoids generated from the confidence intervals for the slope and intercept of each regression.\(^7\) This technique is more powerful than multiple t tests for comparing data sets over a range of the independent variables in that it includes comparisons of the slopes of the entire relationships and the intercepts.

An index of the autoregulatory abilities of the animals was calculated by the following equation\(^1\): autoregulatory index = \[(F_2 - F_1)/(F_2 - F_1)/(P_2 - P_1)/P_1\], where \(F_1\) and \(P_1\) are RBF and renal perfusion pressure at one point on the autoregulatory curve and \(F_2\) and \(P_2\) are the same variables at a second point. A value of zero indicates no change in flow with the change in perfusion pressure, or perfect autoregulation. A value of 1.0 or greater is calculated when the flow change is the same or greater than the fractional change in perfusion pressure, indicating absence of autoregulation.

Results

The slow i.v. infusion of verapamil in the dose used here had only a small effect on mean arterial blood pressure. The control group mean was 100.1 ± 1.9 mm Hg, and the verapamil-treated group mean was 96.5 ± 1.9 mm Hg (\(p = \text{NS}\)). However, the calcium entry blocker did have significant effects on the other measured variables, all of which are presented in Table 1.

RBF at the 100 mm Hg pressure level was greater in the verapamil-treated group than in the control group, the values being 4.49 ± 0.14 and 3.81 ± 0.22

### Table 1. Comparison of Renal Function Data in Control and Verapamil-Treated Groups Over a Range of Renal Perfusion Pressure

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<th>Variable</th>
<th>Perfusion pressure (mm Hg)</th>
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</table>

C = the control group; V = the verapamil-treated group; RBF = renal blood flow; GFR = glomerular filtration rate; RVR = renal vascular resistance; FF = filtration fraction; RR = renin release.
ml/min/g (p<0.020) for the two groups, respectively (Figure 1). Autoregulation of RBF was perfect in the control group from 100 to 90 mm Hg (3.81 ± 0.22 and 3.82 ± 0.20 ml/min/g) and continued to be effective down to 80 mm Hg (index value, 0.144). In the treated group, RBF autoregulation was less effective; the index was 0.401 between 100 and 90 mm Hg and was 0.468 between 100 and 80 mm Hg. Below 80 mm Hg there was no autoregulation in either group, with the indexes being greater than 1.00 in both. There were no significant differences in the mean blood flows at any of the arterial pressure levels below the autoregulatory threshold.

Total renal vascular resistance was significantly (p<0.025) less in the treated group than in the control group only at the 100 mm Hg level (Figure 2). It decreased significantly over the autoregulatory range in the verapamil-treated group as well as in the control group.

The GFR was 51% greater in the verapamil-treated group than in the control group at the 100 mm Hg perfusion pressure level (Figure 3). Although it was poorly autoregulated in the treated group (index between 100 and 80 mm Hg was 0.735), the mean value was significantly greater than that of the control group at each level of perfusion pressure down to 40 mm Hg. The filtration fraction was also greater in the treated group than in the control group, averaging 36.9 ± 1.5% in the verapamil-treated group at 100 mm Hg and 28.5 ± 1.6% in the control group at the same level of perfusion pressure (Figure 4). The difference persisted down to 40 mm Hg.

The differences in renin release rates between the two groups were not significant at the 100 or 90 mm Hg perfusion pressure levels (see Table 1); however, at the 80 mm Hg level the verapamil-treated group's mean release rate was 11.00 ± 4.20 U/min/g, 3.69 times that of the control group (2.98 ± 1.50 U/min/g; p<0.05). At the 50 mm Hg level the treated group mean remained more than two times greater than the control group's rate (p<0.05). The three parameter regressions describing the renin release data are presented in Figure 5. For the control group the equation for the regression is y = 0.016x^2 - 2.87x + 132, in which y represents the renin release rate and x is the arterial perfusion pressure. The correlation coefficient is 0.80. The equation for the regression for the verapamil-treated group is y = 0.012x^2 - 2.67x + 150. The correlation coefficient is 0.68. The two regressions are significantly different (p<0.05).

Discussion

The findings of this study, namely, that verapamil administration resulted in an increase in RBF, GFR, and filtration fraction and a reduction in renal vascular resistance, support the hypothesis that the calcium entry blocker elicits a reduction in preglomerular resistance that is relatively greater than any accompanying postglomerular decrease in resistance. To be more pre-
pressure, but that the difference becomes greater as perfusion pressure is lowered. KW = kidney weight.

The single asterisk at the 80 and 50 mm Hg levels indicates a significant difference (p<0.05). Notice that the release rate from the verapamil-treated group is not different from that of the control group at the higher levels of perfusion pressure, but that the difference becomes greater as perfusion pressure is lowered. KW = kidney weight.

FIGURE 4. Filtration fractions of the control and verapamil-treated groups. The large increase in filtration fraction together with the decrease in vascular resistance (see Figure 2) seen in the verapamil-treated group strongly suggests preglomerular vasodilation. Values are means and SEM. Double asterisk denotes a difference between the group means (p<0.01).

Circ, for the reduction in renal resistance to be accompanied by a large increase in GFR and filtration fraction, verapamil must have caused a change in the preglomerular to postglomerular resistance ratio that strongly favored an increase in filtration. This effect may have included an increase in postglomerular resistance due to the elevated renin release together with a proportionally greater decrease in preglomerular resistance. In addition, verapamil may have had a direct glomerular effect resulting in an increase in the filtration coefficient. A combination of all of these effects may have been involved to produce the large increase in GFR. Only changes in these locations are consistent with the pattern of responses we observed. The magnitude of the increase in GFR, 51% at 100 mm Hg, caused by the verapamil probably was exaggerated by the experimental design; the perfusion pressure was elevated above the normal level for the rabbit of 75 to 80 mm Hg by increased sympathetic nervous system activity due to bilateral carotid occlusion. It is accepted generally that calcium entry blockers have greater effects in vascular beds during periods of high vascular tone, and the kidneys analyzed in this study probably were experiencing adrenergically mediated vascular constriction. Furthermore, Pelayo90 recently has demonstrated in the rat that calcium entry blockers are highly effective in reducing the preglomerular resistance resulting from α-adrenergic sympathetic stimulation. Therefore, the quantitative effect observed in the present study may be considerably greater than that which might be expected in kidneys with normal vascular tone. However, one of the hallmarks of essential hypertension is greatly elevated renal vascular resistance.20

We observed a significant stimulatory effect of verapamil on the renin release rate that was most clearly apparent at reduced perfusion pressure levels. At the 100 and 90 mm Hg levels the release rates of the two groups were not significantly different (see Table 1); however, the difference became progressively greater as perfusion pressure was lowered. This pattern suggests that the calcium entry blocker interacted in a multiplicative fashion with the stimulatory effect of reduced perfusion pressure. There is strong evidence that renin release is inversely related to cytosolic calcium activity in the juxtaglomerular cells,21 to a hypothesis that is consistent with our findings. Additionally, the multiplicative interaction suggested by our data and the plateau seen in the verapamil-treated group's renin release response between 50 and 40 mm Hg (see Table 1) were predicted by a hypothetical model proposed by Fray et al.24 based on changes in cytosolic calcium being the common factor controlling renin release.

The stimulation of renin release may have contributed importantly to the renal hemodynamic alterations we found. If the efferent arteriole is more sensitive than the afferent arteriole to the vasoconstrictor effects of angiotensin II,25 then the elevated renin release rate elicited by the verapamil may have caused an increase in postglomerular resistance that would have contributed to the factors favoring the increase in filtration rate.

Altering renal hemodynamics in a manner that reduces vascular resistance and increases GFR is an ideal maneuver to reduce the steady state level of arterial pressure. With the increase in GFR comes an increase in sodium excretion that persists until sodium and volume depletion lead to reduced arterial pressure. When arterial pressure falls to a point at which GFR and sodium excretion again are at normal rates, a new steady state is established characterized by reduced arterial pressure, normal GFR, and sodium balance. In verapamil-treated patients with essential hypertension, steady state GFR and renal vascular resistance are near
normal in most studies while arterial pressure is reduced.27-29 This response is what would be expected if the primary effect of verapamil were reduction in pre-glomerular vascular resistance. If filtration rate were measured in patients shortly after the start of verapamil treatment, an increase in GFR might be observed if the acute hypotensive effects of the calcium entry blocker were prevented; in several studies in patients, increases in GFR have been reported soon after the start of treatment with the calcium entry blocker.10,11 Much of the clinical data concerning renal function in patients treated with verapamil appear to be consistent with the finding in the present study that verapamil causes a change in renal hemodynamics favoring an increase in filtration. Further support is needed from properly designed clinical and experimental studies for the hypothesis that this change in renal hemodynamics and the associated alteration in GFR regulation is the primary antihypertensive mechanism of verapamil.

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