Effect of Verapamil on Blood Pressure and Lesions in Heart and Kidney of Rats Made Hypertensive by Deoxycorticosterone (DOC)

ARTUR P. AGUAS, MD,
and PETER A. NICKERSON, PhD

Department of Pathology, State University of New York at Buffalo, Buffalo, New York

The effect of verapamil, a calcium antagonist, was studied in rats treated with deoxycorticosterone (DOC). DOC induced hypertensive cardiovascular disease with accompanying gross and microscopic lesions in heart and kidney. Verapamil administered in the drinking fluid (1% sodium chloride) prevented hypertension and significantly ameliorated the incidence and severity of cardiovascular lesions. With exception of the spleen, verapamil did not prevent renal or myocardial hypertrophy in rats treated with DOC in spite of prevention of hypertension. The level of verapamil in the serum of animals consuming verapamil (0.37 ± 0.16 μg/ml) was less than that of the DOC–verapamil group (0.89 ± 0.16 μg/ml), although the difference was not significant. These results confirm the efficacy of verapamil in reducing blood pressure and in ameliorating vascular lesions. (Am J Pathol 1983, 110:48–54)

INCREASED LEVELS of calcium have been reported in vascular smooth muscle cells in different models of experimental hypertension.[1-5] These findings, coupled with the well-established role that calcium plays in the contractile state of smooth muscle, has led some authors to postulate that increased concentration of calcium in the arterial wall is involved directly in the pathogenesis of essential hypertension in humans, the intracellular accumulation of the cation being attributed to an abnormally high sodium–calcium exchange across the plasma membrane.[6,7] These observations appear to make calcium antagonists a logical choice in the therapeutic management of hypertension. Recent experimental and clinical studies have reported on the effectiveness of calcium antagonists in the treatment of hypertension.[8-11] Verapamil is a calcium antagonist that has been approved recently for clinical use in the United States and is useful in treatment of hypertrophic cardiomyopathy,[12,13] coronary arterial disease,[14] and supraventricular arrhythmias.[15] In the present paper we report the effect of chronic intake of verapamil on blood pressure and on the morphologic features of heart and kidney in rats made hypertensive with deoxycorticosterone (DOC). Verapamil administration prevented blood pressure from reaching hypertensive levels, and it had a protective effect on vascular lesions in heart and kidney induced by DOC + saline treatment.

Materials and Methods

Forty-five female Sprague–Dawley rats, 4 weeks of age, were obtained from Holtzman Co., Madison, Wisconsin. All the animals were caged individually in air-conditioned quarters and were divided into 3 groups of 10 (Groups 1–3) and 1 group (Group 4, DOC + verapamil) of 15 rats. One week after arrival, the animals had the right kidney removed under ether anesthesia. The rats in Groups 2 and 4 received subcutaneous implants of a 50-mg pellet of 11-deoxycorticosterone (DOC) (Sigma Chemical Co., St. Louis, Mo) and a similar pellet 2 weeks later. We implanted the pellets by making a 0.5-inch incision on the middle of the back and running a blunt instrument approximately 1.5 inches subcutaneously.

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Address reprint requests to Dr. Peter A. Nickerson, Department of Pathology, State University of New York at Buffalo, Buffalo, NY 14214.

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The pellet was then pushed inward and the incision closed by wound clips. The animals were given Lab Chow *ad libitum* and 1% NaCl (Groups 1 and 2) or 1% NaCl containing 3.6 mg% (wt/vol) verapamil hydrochloride (Isoptin, Knoll Pharmaceutical Co., Whippany, NJ) (Groups 3 and 4) as a drinking solution. The fluid intake of each rat was measured every 2–3 days, when bottles were filled with freshly made solutions. Bottles containing verapamil were wrapped in aluminum foil to avoid exposure to light. Body weight and systolic blood pressure were recorded weekly. Systolic blood pressure was measured in lightly anesthesized animals with a Physiograph 4 (E and M Instrument Co., Houston, Tex) as described previously.[16] Values above 150 mm Hg were considered hypertensive.

Five weeks after the start of the experiment, we killed all the animals by decapitation and took blood samples for evaluation of serum calcium levels, which are determined colorimetrically by the method of Baginski et al,[17] using a 60-second Calcium Kit (American Monitor, Indianapolis, Ind). At necropsy, the hearts and kidneys of all the rats were examined for macroscopic lesions (see Results).[16,18] The percentage of incidence and the severity index of gross and microscopic lesions were calculated. The severity of lesions was graded by a semiquantitative method based on as scale of 0–4+, taking into account the frequency and extent of lesions. We obtained the severity index by dividing the total score for each group by the theoretic maximum score for the group. The organs were removed and fixed in 10% formalin before being weighed and processed by conventional techniques for histologic examination. Dr. Nickerson graded the gross and microscopic lesions without knowledge of the experimental group being assessed (double-blind protocol).

The data were analyzed by one-way analysis of variance. If the F-value was found to be statistically significant, the significance among the individual means was checked with the Bonferroni modification of the *t* test.[19] The serum was analyzed for verapamil by the method of McAllister and Howell.[20] An Aminco-Bowman Spectrophotofluorometer was used at an excitation wavelength of 275 nm and emission wavelength of 310 nm. The percentage of recovery ranged between 85% and 92%. Concentrations of unknown samples were calculated by comparison with standards of verapamil (1.0 μg/ml, 2.5 μg/ml, and 5 μg/ml) in 0.1 N HCl.

Results

Blood Pressure and Body Weight

A significant percentage of rats from Group 2 (DOC + saline) became hypertensive during the last 2 weeks of the experiment (4 and 5 weeks after implantation of DOC). Progressive increase in the values of blood pressure and in the percentage of incidence of hypertensive animals was observed in this group (Table 1). In contrast, all DOC + saline rats that were treated with verapamil (Group 4) were normotensive throughout the experiment; at 4 and 5 weeks the systolic blood pressure of the DOC + verapamil group was significantly less than that of the DOC group and except at 1 and 4 weeks not statistically different from the verapamil group. Verapamil, when given to control (mononephrectomized) rats, did not induce a significant decrease in blood pres-

Table 1—Systolic Blood Pressure of Rats Treated With DOC or Verapamil, Alone or in Combination*

	Week				
	1	2	3	4	5
Group					
Control	96 ± 4†	96 ± 5	110 ± 6	107 ± 3	103 ± 4
DOC	108 ± 5**	112 ± 5‡	134 ± 6‡ (10%)	139 ± 4¶ (40%)	140 ± 6¶ (60%)
Verapamil	88 ± 2**	99 ± 5**	105 ± 3**	98 ± 3**	117 ± 3**
DOC + verapamil	113 ± 3§	112 ± 3§	115 ± 6**	117 ± 3**	115 ± 3**
Additional statistical comparisons					
DOC vs verapamil	$P < 0.01$	NS	$P < 0.01$	$P < 0.001$	$P < 0.01$
DOC vs DOC + verapamil	NS	NS	NS	$P < 0.003$	$P < 0.001$
Verapamil vs DOC + verapamil	$P < 0.006$	NS	NS	$P < 0.001$	NS

* Number in parenthesis represents the percentage of hypertensive animals.
† Mean ± SEM; superscript is comparison with the control group; NS, not significant.
‡ $P < 0.03$.
§ $P < 0.01$.
¶ $P < 0.001$.
** Not significant.

Table 2—Effect of DOC or Verapamil Alone or in Combination on Saline Intake*

	Week				
	1	2	3	4	5
Group					
Control	69.8 ± 5.4†	70.3 ± 6.5	72.1 ± 3.3	76.2 ± 3.6	80.1 ± 4.4
DOC	108.3 ± 2.7§	123.1 ± 9.3§	172.0 ± 13.9§	200.5 ± 12.7§	216.5 ± 12.5§
Verapamil	76.1 ± 6.3** (12.4 ± 2.1)	83.5 ± 8.5** (13.2 ± 3.3)	73.1 ± 4.6** (10.4 ± 1.9)	72.7 ± 2.5** (10.6 ± 1.1)	69.2 ± 1.8** (9.7 ± 0.7)
DOC + verapamil	109.1 ± 4.2§ (18.2 ± 2.0)	120.3 ± 3.9§ (19.3 ± 1.7)	175.0 ± 9.7§ (26.8 ± 2.3)	188.2 ± 3.2§ (31.5 ± 1.3)	191.3 ± 4.6§ (26.9 ± 1.5)
Additional statistical comparisons					
DOC vs verapamil	$P < 0.001$	$P < 0.05$	$P < 0.001$	$P < 0.001$	$P < 0.001$
DOC vs DOC + verapamil	NS	NS	NS	NS	$P < 0.05$
Verapamil vs DOC + verapamil	$P < 0.001$	$P < 0.05$	$P < 0.001$	$P < 0.001$	$P < 0.001$

* Milliliters per day.
† Mean ± SEM; superscript is comparison with the control group; number in parenthesis is verapamil intake mg/kg/day; NS, not significant.
‡ $P < 0.05$.
§ $P < 0.001$.
** Not significant.

sure. Treatment with DOC, verapamil, or both had no significant effect on body weight: at 5 weeks the control group level was 255 ± 8 g; the DOC group level was 245 ± 9 g; the verapamil group level was 258 ± 4 g; and the DOC + verapamil group level was 254 ± 6 g.

Fluid Intake

A significant increase in fluid intake was observed in both DOC-treated groups (2 and 4); the addition of verapamil (Group 4) reduced the consumption of saline slightly, but only significantly at 5 weeks (Table 2). Consumption of saline in the control group (Group 1) and verapamil-treated rats (Group 3) was similar, suggesting that the drug was palatable to the animals. The verapamil received per day by rats from Group 3 was not significantly different from one time to another, whereas the drug intake for rats in Group 4 (DOC treatment) increased steadily for the first 3 weeks, reaching a plateau at the fourth and fifth weeks.

Organ Weights

Kidney weight almost doubled in DOC-treated rats, and a significant increase in weight was also observed in heart, liver, and spleen after DOC treatment (Table 3). Organ weights in the verapamil-treated group (Group 3) were comparable to those of controls (Group 1); with the exception of the spleen, verapamil did not prevent myocardial or renal hypertrophy or increase in weight of the liver after DOC treatment.

Table 3—Effect of Verapamil and DOC Alone or in Combination on Organ Weights (in Milligrams)

	Heart	Kidney	Spleen	Liver	Thymus	Brain	Adrenal Gland	Ovary
Group								
Control	966 ± 29*	1,539 ± 144	657 ± 17	10,591 ± 372	359 ± 26	1,960 ± 45	81 ± 3	97 ± 5
DOC	1,291 ± 34§	2,611 ± 143§	893 ± 90†	13,261 ± 673‡	346 ± 56¶	2,027 ± 52¶	69 ± 3¶	84 ± 9¶
Verapamil	954 ± 36¶	1,516 ± 75¶	713 ± 50¶	10,964 ± 216¶	309 ± 17¶	1,879 ± 55¶	73 ± 5¶	108 ± 6¶
DOC + verapamil	1,189 ± 29§	2,653 ± 94§	687 ± 41¶	12,110 ± 398¶	285 ± 23¶	1,968 ± 22¶	66 ± 2¶	85 ± 5¶
Additional statistical comparisons								
DOC vs verapamil	$P < 0.001$	$P < 0.001$	NS	$P < 0.01$	NS	NS	NS	NS
DOC vs verapamil + DOC	NS	NS	$P < 0.05$	NS	NS	NS	NS	NS
Verapamil vs verapamil + DOC	$P < 0.001$	$P < 0.001$	NS	NS	NS	NS	NS	NS

* Mean ± SEM; superscript is comparison with the control group; NS, not significant.
† $P < 0.03$.
‡ $P < 0.003$.
§ $P < 0.001$.
¶ Not significant.

Table 4—Effect of DOC or Verapamil Alone or in Combination on Percent Incidence and Severity of Gross and Microscopic Lesions in Kidney and Heart

	Gross lesions			
	Kidney		Heart	
Group	% Incidence	Severity index	% Incidence	Severity index
Control	0	0	0	0
DOC	100	0.275	100	0.525
Verapamil	0	0	0	0
DOC + verapamil	13	0.025	60	0.175

	Microscopic lesions						
	Kidney				Heart		
		Severity index				Severity index	
Group	% Incidence	Casts	Glomeruli	Vessels	% Incidence	Scars	Coronary Vessels
Control	0	0	0	0	0	0	0
DOC	100	0.675	0.537	0.287	90	0.187	0.275
Verapamil	0	0	0	0	0	0	0
DOC + verapamil	6	0.137	0.025	0	20	0	0.025

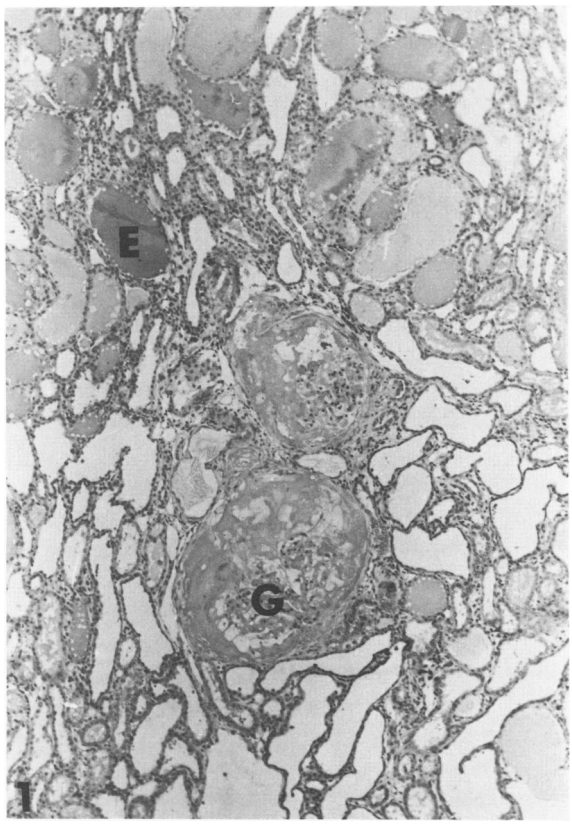

Figure 1—Kidney from a rat treated with DOC. Glomeruli (*G*) are compressed by exudate. Some kidney tubules are filled with eosinophilic casts (*E*), whereas the contents of other tubules do not stain, although they are dilated. (H&E, ×51)

Incidence and Severity of Gross and Microscopic Lesions in Heart and Kidney

All animals from Group 2 (DOC) had focal areas of scars on the epicardial surface of the heart, and the surface of the kidney was granular and showed extensive pinpoint hemorrhages (Table 4). No visible cardiac or renal damage was seen in rats not treated with DOC. When verapamil was added to the saline solution of DOC-treated rats (Group 4), a marked decrease in the incidence and the severity of cardiac and renal lesions was observed. In fact, the incidence of renal and cardiac lesions in DOC-treated rats given verapamil was 13% and 60%, respectively, whereas all the DOC-treated rats not given verapamil had lesions in both organs. Moreover, the severity indices of renal and cardiac lesions were 11 and 3 times lower, respectively, in steroid-treated rats that received verapamil, in comparison with those that did not receive drug therapy (Table 4).

On microscopic examination, eosinophilic casts were present within tubules of the kidney in DOC-treated rats (Figure 1), which on occasion compressed the tubular epithelium. Some glomeruli were completely obliterated by fibrosis, whereas in others, capillary loops were compressed by exudate (Figure 1). Renal lesions in animals that received verapamil and DOC were almost absent, appearing in 6% of the animals (Figure 2).

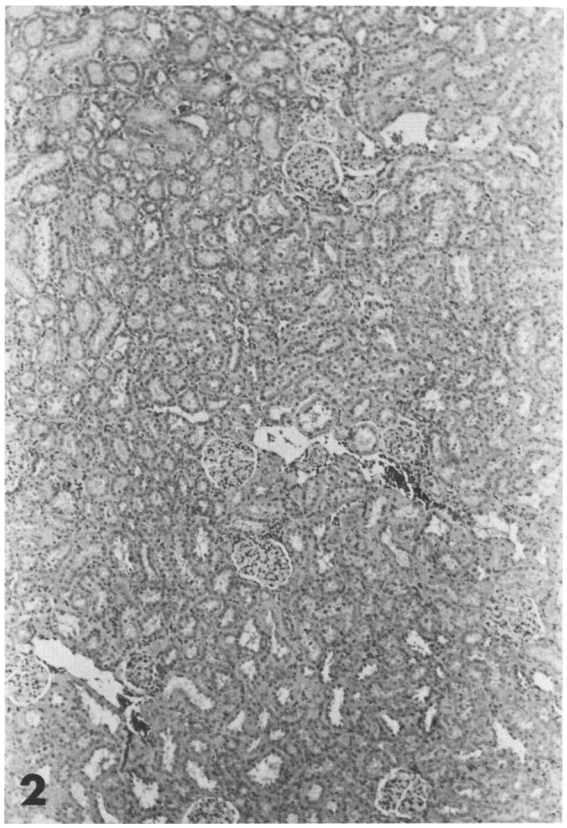

Figure 2—Kidney from a rat treated with DOC and verapamil. Neither vascular lesions nor eosinophilic casts are present. (H&E, ×51)

By light microscopy, the coronary arteries of DOC-treated animals (Figure 3) showed hyalinzation and sclerosis of the media. Focal areas of fibrous connective tissue (scars) were present in the myocardium. A slight hyalinization of the media of a few coronary arteries was observed in the heart of animals receiving verapamil and DOC (Figure 4).

Blood Calcium

Serum calcium in the control group was 11.2 ± 0.3 mg/dl. DOC treatment induced a significant decrease ($P < 0.001$) in the level of calcium (Group 2, 8.8 ± 0.45 mg/dl), also reported by Massingham and Shevde,[2] whereas verapamil administration to DOC-treated rats tended to prevent this change (Group 4, 10.6 ± 0.4 mg/dl). A slight but not significant decrease in blood calcium was observed when verapamil was given to untreated animals (Group 3, 10.3 ± 0.3 mg/dl).

Verapamil Levels

The level of verapamil in the serum of animals consuming saline-verapamil solution was 0.37 ± 0.16 μg/ml, whereas in the saline-verapamil-DOC group it was 0.89 ± 0.16 μg/ml. The difference between the two groups was not significant, although it was close to being statistically significant ($P < 0.1$).

Discussion

Calcium-blocking agents such as verapamil have the potential for use in the therapeutic management of arterial hypertension. Verapamil has a potent hypotensive effect when administered intravenously,[21,22] an action particularly useful in the treatment of acute hypertensive crises.[23] We designed the present experiment to investigate the effect of chronic oral intake of verapamil both on blood pressure and on cardiac and renal lesions of rats made hypertensive by subcutaneous implantation of deoxycorticosterone (DOC) and intake of saline. DOC-treated animals, or experimental models where excess DOC is synthesized and secreted, provide a model of mineralocorticoid hypertension that has been studied in our laboratory.[24-25] DOC treatment of the rats (Groups 2 and 4) resulted in saline polydipsia and organ weight changes similar to those previously reported in steroid-treated animals.[26-29] The mean of the blood pressure in the DOC-

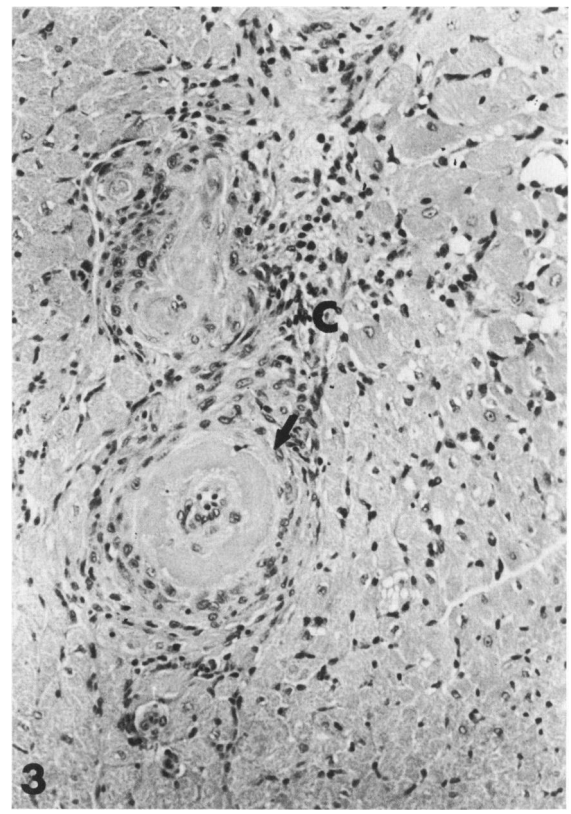

Figure 3—Myocardium from a rat treated with DOC. The media of coronary arteries is hyalinized (*arrow*). Foci of chronic inflammatory cells (*C*) are present near the coronary arteries. (H&E, ×180)

treated animals did not reach hypertensive levels at 5 weeks; this is attributable to the fact that only 60% of the animals achieving pressure above 150 mm Hg. Lesions, however, were present in 100% of the animals. This observation is probably attributable to the depression of blood pressure by the light ether anesthesia utilized in the present study. Recent unpublished studies in our laboratory and in a previous report[30] on DOC-induced hypertension show a significant reduction of blood pressure by ether as compared with pressure recorded in conscious animals.

A significant reduction in the rise of blood pressure was observed in DOC–saline-treated rats that received verapamil. In fact, the drug was effective in maintaining blood pressure within the range of normotensive values. This observation confirms the efficacy of verapamil in reducing blood pressure. A possible explanation for the finding is a blockage of the calcium channel by verapamil in vascular smooth muscle.[22]

In spite of the reduction in blood pressure of the verapamil–DOC group, the weights of the kidneys and the hearts of the verapamil–DOC group were comparable to those of the DOC group; this observation may reflect an effect of DOC which is not affected by simultaneous treatment with verapamil. Myocardial hypertrophy has been reported in spontaneously hypertensive rats despite the return of blood pressure to within the normal range.[31] Tomanek[32] reported cardiac hypertrophy in 50% of 4-month-old animals and in 42% of 7-month-old animals in spite of the return of blood pressure to within the normal range in treated rats. Kidney weight was not decreased in spite of the reduction of blood pressure in DOCA-induced hypertension with an antagonist (progesterone).[33]

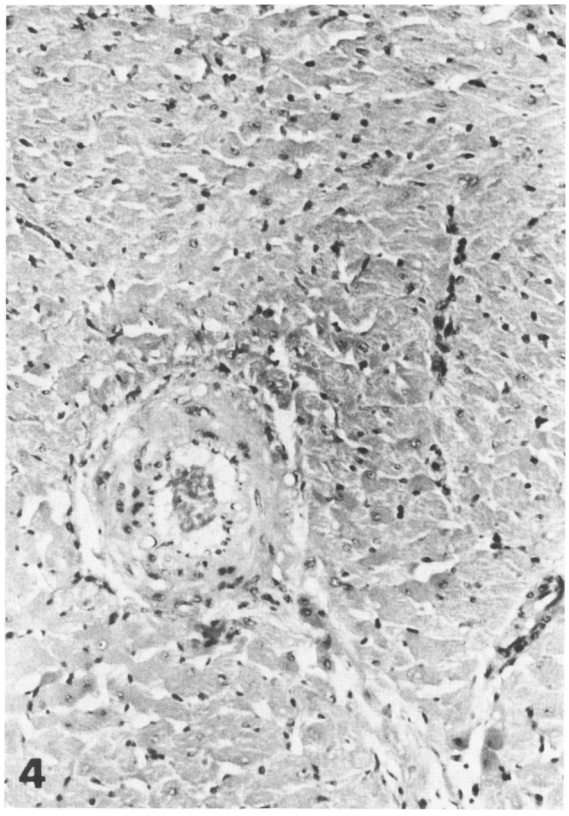

Figure 4—Myocardium from a rat treated with DOC and verapamil. No vascular lesions are present. (H&E, × 180)

Verapamil appears to have an important effect in the prevention of cardiac and renal lesions consequent to implantation of DOC. In fact, an almost complete absence of renal lesions and a marked decrease in the incidence and severity of pathologic cardiac changes was seen in the DOC–salt-treated rats treated with verapamil. One interpretation of the results is that the decrease in cardiac and renal lesions results from a reduction in pressure overload on the vascular system. There has been controversy over whether cardiac and renal lesions are caused directly by the pressure alone[34] or in combination with other factors.[35] It was not possible to resolve this question in the present study. An interaction of DOC, sodium, calcium, and verapamil at the level of the smooth muscle cell, however, may well be involved in reduction of the lesions. Reduction of intracellular calcium by verapamil may alter the contractility of vascular smooth muscle,[36] explaining, at least in part, the reduction of vascular lesions. A previous study from our laboratory,[18] in which parathyroidectomy, in spite of an elevated systolic blood pressure, ameliorated the vascular lesions induced by DOC, supports this conclusion. In the heart, it should also be noted that reduction in the cellular demand for oxygen is induced by the drug.[37] Support for this assumption is found in the study by Smith et al[38] of experimental myocardial infarction, which showed that verapamil reduced infarct size and incidence of sudden death.

Caution is needed in the extrapolation of our results to human therapy for hypertension, because the dose of verapamil we have used in the present study is higher than that allowed in man.[39] However, the effect of verapamil in preventing hypertensive lesions in the vessels of the heart and the kidney in the present study suggests that the drug may be effective in controlling the complications of hypertension.

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