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Cardiovascular Effects of a *Trandolapril/Verapamil* Combination in Patients With Mild to Moderate Essential Hypertension

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Single drug therapy for patients with uncomplicated mild to moderate essential hypertension can provide adequate blood pressure (BP) reduction in no more than 40% to 60% of the population, depending on drug dosage and demographic characteristics of the study group.[1] Thus, adequate BP control will require the addition of a second agent in a large number of patients. Among the various possible combinations of antihypertensive agents, angiotensin-converting enzyme inhibitors and calcium antagonists appear to be particularly attractive because these drugs have different effects on the cardiovascular system, thereby theoretically improving BP response and minimizing adverse effects.[2,3] This study evaluates the cardiovascular effects of trandolapril, a new nonsulfhydryl long-acting angiotensin-converting enzyme inhibitor, in combination with slow-release verapamil in a fixed dose preparation.

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Fourteen patients with stage I to II essential hypertension were included in the study. Demographic data of the patients are summarized in Table I. The patients had either never received antihypertensive therapy or had all antihypertensive medication discontinued before a 4-week placebo run-in phase. Patients with secondary forms of hypertension, based on history, physical examination, and routine blood work were excluded. To qualify for study inclusion, patients must have had a supine diastolic BP between 95 and 114 mm Hg during 2 consecutive visits in the last 2 weeks of the placebo run-in phase. After the baseline hemodynamic assessment, all patients were started on 2 mg of trandolapril/180 mg verapamil SR once daily. If a successful therapeutic response (supine diastolic BP <85 mm Hg) was not achieved after 2 weeks, the dose was increased to 4 mg trandolapril/240 mg verapamil SR once daily and then to 2 mg trandolapril/180 mg verapamil SR twice daily after an additional 2 weeks if needed. Each patient was maintained at the dose in which a successful therapeutic response was achieved and was treated for a total of 12 weeks. Each subject provided informed written consent to a protocol previously approved by the Institutional Clinical Investigation Committee.

TABLE I Patient Demographics

Age (yr)	57 ± 12
Sex (men/women)	7/7
Race (white/black)	7/7
Weight (kg)	77.3 ± 14.0
Height (cm)	170.4 ± 10.4
Body surface area (m^2)	1.89 ± 0.22
Body mass index (kg/m^2)	26.4 ± 2.56

Data are expressed as mean ± SD.

After 4 weeks of the placebo run-in phase and at the end of the study, patients were studied in the hemodynamic laboratory after an overnight fast as previously described.[4] Briefly, an arterial catheter was placed in the aortosubclavian junction, and a venous catheter was placed in the superior vena cava by the modified Seldinger technique. Continuous recording of arterial BP was obtained by a Statham P-23 pressure transducer, and simultaneous heart rate was monitored by electrocardiogram (lead II).

Plasma volume was measured during the hemodynamic study with 125-iodine-labeled albumin. Total blood volume was estimated from plasma volume and total body hematocrit:

$$\text{total blood volume} = \frac{\text{plasma volume}}{1 - (\text{hematocrit } 0.91)},$$

with 0.91 being the correction factor for total body hematocrit. Renal blood flow was determined by measuring the clearance of 131-iodine para-aminohippuric (PAH) acid.

In all 14 patients, a 2-dimensional–guided, M-mode echocardiographic tracing of acceptable quality was obtained before and after therapy by use of

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TABLE II Hemodynamic Effects of Trandolapril/Verapamil

	Baseline	Treatment	p Value
Systolic blood pressure (mm Hg)	167 ± 30	147 ± 24	<0.001
Diastolic blood pressure (mm Hg)	101 ± 9	88 ± 10	<0.001
Mean arterial pressure (mm Hg)	123 ± 14	108 ± 12	<0.001
Heart rate (beats/min)	72 ± 8	68 ± 11	0.24
Cardiac output (L/m)	4.82 ± 1.38	4.90 ± 1.63	0.84
Stroke volume (ml/beat)	68 ± 22	72 ± 20	0.34
Total peripheral resistance (U)	28 ± 4	24 ± 5	0.10

Data are expressed as mean ± SD.

TABLE III Effect of Trandolapril/Verapamil on Left Ventricular Structure and Function

	Baseline	Treatment	p Value
Septal wall thickness (mm)	12.5 ± 2.6	11.5 ± 2.4	0.007
Posterior wall thickness (mm)	12.0 ± 2.5	11.1 ± 2.4	0.009
Diastolic dimension (mm)	46.0 ± 5.7	46.7 ± 5.7	0.40
Systolic dimension (mm)	28.1 ± 5.1	27.6 ± 5.9	0.58
Relative wall thickness (%)	53 ± 13	48 ± 11	0.04
Left ventricular mass (g)	275 ± 104	250 ± 95	0.007
Left ventricular mass index (g/m^2)	144 ± 46	131 ± 43	0.004
Ejection fraction (%)	68 ± 10	70 ± 10	0.37
Endocardial fractional fiber shortening (%)	39 ± 8	41 ± 8	0.35
Midwall fractional fiber shortening (%)	14.6 ± 3.0	16.3 ± 3.3	0.05
Percent of predicted midwall fractional fiber shortening (%)	79.3 ± 16	87.4 ± 18	0.06
End-systolic wall stress (U)	36.2 ± 12.4	32.8 ± 12.2	0.16

Data are expressed as mean ± SD.

TABLE IV Effect of Trandolapril/Verapamil on Fluid Volume State and Renal Function

	Baseline	Treatment	p Value
Body weight (kg)	77.3 ± 14	77.3 ± 14	0.98
Total blood volume (ml)	5,003 ± 1,179	5,176 ± 1,303	0.45
Plasma volume (ml)	3,123 ± 749	3,233 ± 755	0.47
PAH clearance (ml/min)	475 ± 149	481 ± 165	0.85
Renal blood flow (ml/min)	777 ± 289	773 ± 274	0.92
Renal vascular resistance (U)	182 ± 74	158 ± 63	0.10

Data are expressed as mean ± SD.
PAH = para-aminohippuric acid.

an ultrasonoscope (Toshiba SSA-60A, Nasu, Japan) interfaced with a line scan recorder (LSR-20B) and a probe of either PSB-25A 2.5 MHz or PSB-37A 3.75 MHz. Tracings were recorded at a paper speed of 50 to 75 mm/s in the end-expiratory phase with simultaneous electrocardiographic lead. The technique for visualization of the left ventricle has been described previously.[5] Each echo tracing was coded and was read in a blinded manner by 2 investigators; the average value was taken for the calculations. The measurements were obtained according to the guidelines of the American Society of Echocardiography.[6] Because left ventricular (LV) mass by American Society of Echocardiography conventions systematically overestimates the true anatomic LV weight, the values for LV mass were corrected using an equation derived from a comparison of echocardiographic mass with necropsy findings.[7] Systolic LV function was estimated by calculating ejection fraction, endocardial fractional fiber shortening, midwall fractional fiber shortening as described by De Simone et al,[8] and the percentage of predicted midway fiber shortening according to meridional end-systolic wall stress.[8] Stroke volume was estimated using the Teichholz correction of the cube formula[9] and used to calculate cardiac output and peripheral resistance; LV volumes, stroke volume, and cardiac output determined by this method have been shown to be accurate in patients with symmetrically contracting ventricles.[10]

All data are expressed as mean ± SD. One-way analysis of variance with repeated measurements was used to compare baseline values with those after treatment.

During 12 weeks of therapy with trandolapril/verapamil, no important adverse effects were observed, and all 14 patients finished the study. The hemodynamic effects of trandolapril/verapamil combination therapy are listed in Table II. A significant decrease in systolic, diastolic, and mean arterial BP was observed, whereas heart rate was not altered significantly. The decrease in arterial BP appeared to be mediated mainly through a decrease in total peripheral resistance, although the differences did not reach statistical significance (Table II). In contrast, no changes were noted in cardiac output and stroke volume.

The effects of trandolapril/verapamil therapy on LV structure and function are summarized in Table III. Although LV internal diameters remained unchanged, 12 weeks of treatment resulted in a significant decrease in septal and posterior wall thickness. These changes resulted in a significant decrease in relative wall thickness and LV mass. The evaluation of systolic function after therapy showed no significant changes for ejection fraction or fractional fiber shortening measured at the endocardium; however, when midwall fractional fiber shortening was used to evaluate systolic function, a small but significant improvement was observed. Table IV shows the effect of trandolapril/verapamil on fluid state and parameters of renal function. No differences in total body volume, plasma volume, renal blood flow, or PAH clearance were evident after therapy; there was a trend toward decreased renal vascular resistance.

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The results of this study show that the combination of trandolapril and verapamil effectively lowers arterial blood pressure mainly by reducing total pe-

ripheral resistance. Heart rate and stroke volume, however, were entirely unchanged, leaving cardiac output unaltered. These results are in good agreement with previous hemodynamic evaluations of the single compounds[11–14] and combinations of other angiotensin-converting enzyme inhibitors and calcium antagonists,[15,16] although some studies report a mild increase in cardiac output with this combination.[17] Evaluation of cardiac structure showed a marked reduction in LV mass with trandolapril/verapamil combination therapy. This effect was exclusively mediated by reduction in septal and posterior wall thickness; LV internal diameters remained unchanged. The overall decrease in LV mass after 3 months of therapy was about 10%, which is comparable to the reduction in LV mass seen with angiotensin-converting enzyme inhibitors or calcium antagonists alone.[18,19] This indicates that reduction in LV mass may be primarily dependent on reduction in arterial blood pressure rather than nonhemodynamic effects of the individual drugs. Duration of therapy is a very important factor in regression of LV hypertrophy, and therefore, significant advantages of an angiotensin-converting enzyme inhibitor/calcium antagonist combination may not become evident until later in the course of therapy.[20]

The results of the present study indicate that reduction of LV mass with a combination of angiotensin-converting enzyme inhibitor and calcium antagonist is associated with a small but significant improvement in systolic performance as measured by midwall fractional fiber shortening. This parameter takes into account the epicardial migration of the midwall during systole, and has been regarded as the physiologically more appropriate assessment of systolic performance, particularly in patients with LV hypertrophy.[8] The improvement in systolic function is likely related to the altered LV structure after sustained decrease in blood pressure rather than a positive inotropic effect of the drugs. In an earlier study, calcium antagonists alone did not improve midway fractional fiber shortening despite a significant decrease in LV mass, suggesting a negative inotropic effect on the myocardium when given alone.

Total blood volume and plasma volume were unchanged after 12 weeks of combination therapy, indicating that the known mild natriuretic effect of verapamil was not amplified by the additional blockade of the renin-angiotensin-aldosterone system.[3,11,12] Also, no significant changes were observed in renal blood flow despite a trend toward decreased renal vascular resistance, which is in agreement with previous studies.

In summary, the combination of trandolapril and verapamil appears to be a useful therapy in patients with mild to moderate essential hypertension. It was well tolerated and, in this study, was without adverse effects. In addition, LV mass decreased significantly, systolic performance improved, and fluid volume state was unchanged. For these reasons, fixed combination therapy with trandolapril and verapamil may be an attractive means of antihypertensive therapy.

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