PHARMACODYNAMICS AND DRUG ACTION

Hemodynamic effects of quinapril, a novel angiotensin-converting enzyme inhibitor

The hemodynamic effects of quinapril, a novel nonsulfhydryl-containing angiotensin-converting enzyme (ACE) inhibitor, were assessed in 10 patients with mild-to-moderate essential hypertension. Compared with placebo, quinapril (20 mg) administered twice daily for 4 weeks significantly lowered blood pressure by decreasing total peripheral resistance without producing tachycardia, an increase in cardiac output, or a rise in plasma catecholamines. Quinapril significantly reduced renal, but not forearm, vascular resistance. Renal blood flow, glomerular filtration rate, and filtration fraction remained unchanged. Left ventricular wall stress was markedly reduced by quinapril, but during the relatively short treatment period, only a nonsignificant trend toward reduction in left ventricular mass was observed. These findings suggest that quinapril is an effective antihypertensive agent that lowers peripheral resistance without increasing cardiac output or disturbing autoregulation of renal hemodynamics. (CLIN PHARMACOL THER 1990;48: 41-9.)

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The hemodynamic hallmark of untreated essential hypertension is increased vascular resistance in most vascular beds.[1] Even in relatively young patients (20 to 40 years of age) with mild hypertension, in whom the typical hemodynamic pattern is an increased cardiac index during rest with almost normal total peripheral resistance, exercise fails to lower total peripheral resistance as much as it does in normotensive age-matched control subjects. In addition, subnormal stroke index and cardiac index can be demonstrated in such patients during exercise.[2] When hypertension is left untreated, the hemodynamic pattern changes over time, evolving toward a "low cardiac output–high resistance" pattern with reduced left ventricular compliance and left ventricular hypertrophy in a large fraction of the patients.[3] These are the changes we would like to prevent or reverse with antihypertensive treatment.

Currently available antihypertensive drugs lower blood pressure through widely different hemodynamic mechanisms. In general, β-adrenoreceptor blockers tend to result in a chronic depression in cardiac output, particularly during exercise,[4] and may lead to less physical endurance during severe work loads.[5-7] In contrast, α-adrenoreceptor blockers, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors reduce vascular resistance and maintain blood flow,[8-14] but the degree of counteracting reflex tachycardia and increase in cardiac output varies widely.

It is likely that the blood pressure lowering effect of ACE inhibitors is mediated largely by withdrawal of the vasopressor influences of angiotensin II,[15,16] although other mechanisms such as bradykinin potentiation may participate.[17,18] Both angiotensin II withdrawal and bradykinin increase would result in dilation of the arteriolar resistance vessels. Quinapril hydrochloride (Cl-906) is a new potent, orally active, nonsulfhydryl, nonpeptide ACE inhibitor developed for the treatment of hypertension and congestive heart failure. Quinapril is converted in vivo to its active metabolite, quinaprilat, which is primarily responsible for its potent ACE inhibition. Clinical studies indicate that quinapril is an effective antihypertensive agent when administered once or twice daily.[19] The acute hemodynamic effects of quinapril have been studied in patients with congestive cardiac failure.[20] However, there is little information on the chronic hemodynamic effects of quinapril in patients with hypertension. Therefore, the aim of the

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present study was to compare the hemodynamic effects of quinapril with placebo during long-term (4 weeks) treatment of patients with mild-to-moderate essential hypertension in a double-blind, randomized crossover design.

MATERIAL AND METHODS

Patients. Ten white men averaging 42 ± 3 years of age (range, 32 to 61 years) with uncomplicated mild-to-moderate essential hypertension were studied. Initial body weight averaged 83 ± 5 kg, and height averaged 166 ± 5 cm. After informed consent was obtained from the subjects, all antihypertensive medications were discontinued for 3 weeks, and patients were included if they had stable diastolic blood pressure between 95 and 115 mm Hg at home (sitting) and in the outpatient clinic (supine) at the end of this period. Average values for their sitting blood pressure in the outpatient clinic at this time were 149 ± 4 mm Hg for systolic, 106 ± 2 mm Hg for diastolic and 120 ± 3 mm Hg for mean blood pressure. Aside from essential hypertension, no subject had any other acute or chronic illness except for one patient who was receiving stable thyroid hormone replacement. Physical examination, ECG, urinalysis, blood counts, and blood biochemistries (including liver and renal function tests) were done to exclude any other concomitant illness or cause of secondary hypertension. The patients were all nonsmokers and were known not to abuse alcohol or drugs. They were urged not to make any changes in their dietary, smoking, or alcohol consumption habits during the entire period of the study.

Protocol. The study was approved by the Human Subject Review Committee of the University of Michigan (Ann Arbor, Mich.). After an initial 3-week washout period without antihypertensive treatment, the patients were randomized to a double-blind, two-period crossover trial comparing quinapril and placebo. Quinapril 20 mg twice a day or matching placebo twice a day (both provided by Warner Lambert/Parke-Davis, Ann Arbor, Mich.) were each given for 4 weeks. Adherence to the study protocol was monitored by having the patients keep a diary and by tablet counting by the investigators. For safety reasons potential side effects or adverse reactions were monitored by asking the patients to make notes in the diary, by direct questioning by the investigator, and by drawing blood for routine chemistry including liver enzymes before and after 1 and 4 weeks in both treatment periods. On the last day of each 4-week period, patients were admitted to the University of Michigan Clinical Research Center for 4 hours. They were instructed not to take over-the-counter medications except acetaminophen for at least 10 days. Only one patient was studied each day beginning at 8 AM, and all studies were performed by the same physicians.

After an overnight fast, that is, 12 hours after taking the last PM dose of the medication, subjects were placed at supine rest in a quiet room where temperature was strictly standardized to 75° F (23.9° C). They were allowed to watch television. A short teflon catheter was initially placed into an antecubital vein of the right arm of each subject and was kept open with a 10 ml per hour infusion of 0.9% sodium chloride. Blood pressure was measured in the right arm as the average of two readings by use of a newly calibrated mercury sphygmomanometer, and heart rate was calculated from the average of 20 to 40 beats taken from the ECG.

Forearm blood flow (FBF) was also measured as the average of two readings by mercury-in-Silastic strain gauge, venous occlusion plethysmography by use of the EC-4 plethysmograph and E-10 rapid cuff inflator (Hokanson Instruments, Issaquah, Wash.). This technique has previously been described in detail and evaluated in our laboratory.[21] The left arm was supported above heart level, and the strain gauge placed around the forearm, approximately 7 cm below the olecranon. Hand blood flow was arrested by a pediatric-sized cuff inflated to suprasystolic pressure at the wrist 60 seconds before FBF determinations. A second cuff on the arm was subsequently inflated to 40 to 50 mm Hg for 10 to 15 seconds and deflated for 5 seconds or more before the next measurement. Forearm blood flow (ml/100 ml forearm volume per minute) was calculated from the mean vertical deflection per minute on the tracings divided by the 1% electrical calibration signal. Forearm vascular resistance (FVR) was calculated as mean arterial blood pressure (MAP) determined during the procedure divided by FBF.

After measuring baseline blood pressure, heart rate, and FBF, the morning dose of medication (quinapril or placebo) was given with 100 ml water. Thereafter, blood pressure, heart rate, and FBF were measured every ½ hour throughout, and hemodynamic profiling was done 2 to 4 hours after the medication was administered. Clinical studies in patients with hypertension have demonstrated that peak change in diastolic blood pressure following quinapril administration occurs at 2 to 4 hours after administration of the dose (Parke-Davis, data on file). Therefore this time frame was chosen to determine peak hemodynamic and blood pressure changes after quinapril administration.

Cardiac output was measured 3 hours after dose administration by an echocardiographic Doppler

Table I. Blood pressure, heart rate, forearm blood flow, and forearm vascular resistance for subjects in the supine position for 4 hours after taking the study medication at 8 AM

	0 Minutes	*30 Minutes*	*60 Minutes*	*90 Minutes*	*120 Minutes*	*150 Minutes*	*180 Minutes*	*210 Minutes*	*240 Minutes*
Systolic blood pressure (mm Hg)									
Placebo	151 ± 6	149 ± 6	149 ± 5	148 ± 6	150 ± 6	151 ± 5	150 ± 5	151 ± 5	152 ± 5
Quinapril	135 ± 5*	134 ± 5†	135 ± 6†	134 ± 5*	134 ± 6*	136 ± 6*	136 ± 5*	137 ± 6‡	139 ± 5‡
Diastolic blood pressure (mm Hg)									
Placebo	102 ± 3	102 ± 3	103 ± 3	102 ± 3	104 ± 3	104 ± 3	105 ± 3	106 ± 3	106 ± 3
Quinapril	93 ± 4*	94 ± 4*	95 ± 3†	94 ± 3*	95 ± 3†	94 ± 3†	94 ± 3†	96 ± 3*	98 ± 3*
Heart rate (beats/min)									
Placebo	66 ± 3	65 ± 3	65 ± 3	64 ± 3	65 ± 3	66 ± 3	66 ± 3	67 ± 3	70 ± 4
Quinapril	66 ± 3	65 ± 2	64 ± 3	63 ± 2	63 ± 2	66 ± 3	65 ± 2	68 ± 3	68 ± 3
Forearm blood flow (ml/100 ml forearm volume/min)									
Placebo	2.9 ± 0.5	2.5 ± 0.4	2.8 ± 0.4	3.0 ± 0.5	3.2 ± 0.5	3.0 ± 0.5	3.0 ± 0.3	3.2 ± 0.6	3.1 ± 0.5
Quinapril	2.8 ± 0.4	3.4 ± 0.9	3.4 ± 0.9	3.2 ± 0.6	2.9 ± 0.4	3.2 ± 0.5	2.9 ± 0.4	3.1 ± 0.5	3.0 ± 0.4
Forearm vascular resistance (arbitary units)									
Placebo	41 ± 6	47 ± 9	42 ± 7	39 ± 9	37 ± 7	40 ± 12	40 ± 7	38 ± 11	39 ± 11
Quinapril	38 ± 4	32 ± 6	32 ± 7	33 ± 5	37 ± 5	34 ± 9	37 ± 5	35 ± 5	37 ± 5

Data are mean values ± SE (n = 10).
*$p < 0.01$; †$p < 0.001$; ‡$p < 0.05$ (quinapril versus placebo).

technique utilizing an ATL Ultramark IV (Bellevue, Wash.). This method has previously been validated against dye dilution in our laboratory.[22] Two-dimensional images of the aortic root were recorded in the long-axis view by use of a 2.25 MHz transducer. The aortic root diameter was measured from the two-dimensional image at the level of the aortic leaflets during mid-systole and the aortic cross-sectional area was calculated. Aortic outflow measurements were obtained from the suprasternal notch with a continuous wave Doppler transmitter operating at 3.0 MHz. The cardiac output and stroke volume measurements were calculated by use of a computer-interfaced digitizing tablet and Doppler analysis program (Freeland Medical Systems, Indianapolis, Ind.). The average of eight consecutive cardiac cycles was taken, and only those Doppler recordings that showed maximal flow velocities and exhibited the "cleanest" envelopes were chosen. The flow velocity integral (FVI), or the area under the velocity curve was determined by tracing from the baseline around the maximal velocity curve. Heart rate was measured from the RR interval of the simultaneously recorded ECG. Stroke volume was calculated by use of the formula:

$$SV\ (ml) = FVI\ (cm) \times CSA\ (cm^2)$$

Cardiac output was calculated by multiplying stroke volume (SV) by heart rate. Cardiac index (CI, $L/min/m^2$) was calculated as the ratio of cardiac output to body surface area estimated from height and weight in conventional tables. Total peripheral resistance index (TPRI) was calculated as MAP/CI. Left ventricular mass (LVM) was calculated by use of the formula:

$$LVM\ (gm) = 1.04\ [(\text{left ventricular internal diameter} + \text{left ventricular septal thickness} + \text{posterior wall thickness})^3 - (\text{left ventricular internal diameter})^3] - 13.6$$

Ejection fraction was determined by use of the formula:

$$[\text{LV internal diameter (diastole)}]^3 - [\text{LV internal diameter (systole)}]^3 / [\text{LV internal diameter (diastole)}]^3 \times 100$$

Left ventricular mass and ejection fraction measurements were obtained from M-mode echocardiographic recordings. Left ventricular peak systolic wall stress was calculated as follows:

$$1.332 \times \text{systolic BP} \times D/4\ h\ (1 + h/D)\ 10^3\ dynes/cm^2$$

Table II. Echocardiographic and Doppler measurements done with the subjects in the supine position 3 hours after dose administration to subjects receiving long-term treatment with quinapril and placebo

	Placebo	*Quinapril*
Cardiac output (L/min)	4.74 ± 0.25	4.78 ± 0.19
Stroke volume (ml/min)	75.7 ± 4.2	74.9 ± 3.4
Ejection fraction (%)	76.3 ± 2.6	73.6 ± 2.9
Left ventricular mass (gm)	220 ± 19	210 ± 14
Left ventricular wall stress (10^3 dynes/cm^2)	170 ± 8	149 ± 9*

Data are mean values ± SE (n = 10).
*$p < 0.01$.

in which D is the left ventricular diameter (diastole) and h is the [interventricular septum thickness (diastole) + LV posterior wall (diastole)]/2. All the echocardiographic and Doppler examinations were performed by the same technician.

Plasma clearance of para-aminohippuric acid (PAH) was measured by a steady-state infusion method[23,24] as an estimate of effective renal plasma flow (RPF). PAH (20 mg/ml, MSD, West Point, Pa.) was mixed in 5% dextrose solution at a final concentration of 8 mg/ml, and 8 mg PAH per kilogram of body weight was given as a rapid infusion over 10 minutes followed by a sustaining infusion for 1 hour, from 2½ to 3½ hours after giving the dose of quinapril or placebo. The sustaining infusion rate of PAH was calculated from the formula:

$$\text{Infusion rate of PAH} = CL_{PAH} \times P_{PAH}$$

in which CL_{PAH} is the estimated clearance of PAH (750 ml/min/1.73 m^2), and P_{PAH} is the target plasma PAH (0.02 mg/ml).

Blood for analysis of plasma PAH was drawn immediately before giving PAH intravenously through the indwelling catheter in the right antecubital vein (plasma blank) and at the end of the 1 hour of intravenous infusion of PAH (steady-state level) by direct puncture of the left antecubital vein with a heparinized vacutainer. Plasma concentration of PAH was determined by colorimetric assay. PAH clearance was calculated as the ratio of infusion rate and difference in plasma concentration of PAH between the two blood samples. Hematocrit was obtained by use of a Coulter Counter M4 30 (Coulter Electronics, Inc., Hialeah, Fla.), and renal blood flow (RBF) was calculated as RPF/1 − hematocrit. Renal vascular resistance (RVR) was calculated as MAP/RBF.

Endogenous creatinine clearance was measured to estimate glomerular filtration rate (GFR). The subjects collected a 24-hour urine specimen for determination of creatinine and volume immediately before each study in the Clinical Research Center. Blood for serum creatinine was sampled concomitantly with the first blood sample for PAH. At this time point, blood was also drawn on EGTA and glutathione for the analysis of plasma catecholamines. This blood sample was kept on melting ice until separation of plasma shortly; plasma was frozen and catecholamines analyzed with the radioenzymatic method of Peuler and Johnson.[25]

Statistical analysis. Data are given as mean values ± SE. Blood pressure and vascular resistance were postulated to decrease in subjects receiving quinapril compared with placebo; therefore differences in these variables were tested by one-tailed tests; other differences were tested by two-tailed parametric tests for single or repeated measurements. Correlation coefficients *(r)* were calculated by use of the least-squares method. A p value less than 0.05 was considered to be the limit for statistical significance.

RESULTS

All the patients entered into the study completed the trial without notable side effects or adverse reaction. The data were tested for an order of treatment effect. Because this could not be found, further analyses were done by comparing the quinapril with the placebo period, regardless of the order in which they were given.

Blood pressure. Systolic, diastolic, and mean blood pressure were all highly significantly lower on quinapril compared with placebo ($p < 0.001$, ANOVA). As shown by Table I, blood pressure was significantly lower in subjects receiving quinapril compared with placebo at all time points during the 4-hour period in the Clinical Research Center. Systolic and diastolic blood pressure differences between the two treatments before and 3 hours after the medication was given were 16.4 ± 4.2/9.5 ± 2.6 and 14.0 ± 3.8/10.8 ± 2.3 mm Hg, respectively.

Six of the subjects responded with an average decrease in mean blood pressure of more than 10 mm Hg, and two subjects responded with an average decrease in mean blood pressure between 5 and 10 mm Hg. After 4 weeks of twice-daily quinapril therapy, further reductions in blood pressure were not observed during the 4-hour interval after quinapril dosing.

Heart rate and plasma catecholamines. Heart rate did not show any significant difference between the two treatments (Table I). Plasma norepinephrine drawn 2.5 hours after dose administration averaged 220 ± 25 versus 202 ± 16 ng/L for subjects receiving quinapril and placebo, respectively (not significant), and plasma epinephrine was 45 ± 5 versus 47 ± 10 ng/L (not significant).

Forearm blood flow and forearm vascular resistance. Repeated measurement analysis of variance (ANOVA) did not reveal any statistically significant difference for FBF or FVR (Table I) during placebo and quinapril treatments.

Cardiac index and total peripheral resistance index. Cardiac function did not change significantly in subjects receiving quinapril treatment compared with placebo (Table II). Cardiac index averaged 2.51 ± 0.09 versus 2.48 ± 0.09 L/min/m^2 body surface area 3 hours after dose administration on the two treatments, respectively (Fig. 1). As also shown in Fig. 1, TPRI was lower

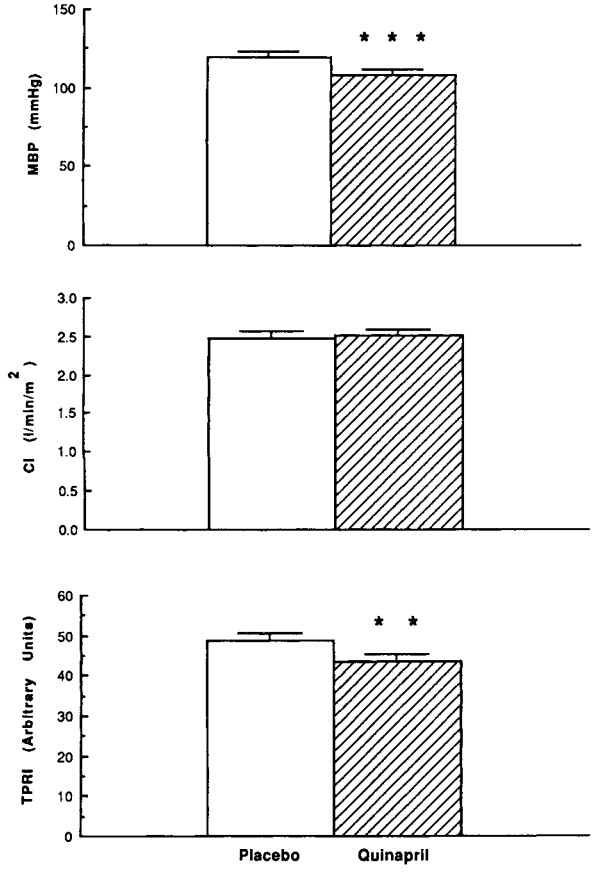

Fig. 1. Effects of quinapril on mean blood pressure (MBP), cardiac index (CI), and total peripheral resistance index (TPRI). Results are mean values + SE (n = 10). **Significantly different from placebo at $p < 0.01$; ***significantly different from placebo at $p < 0.001$.

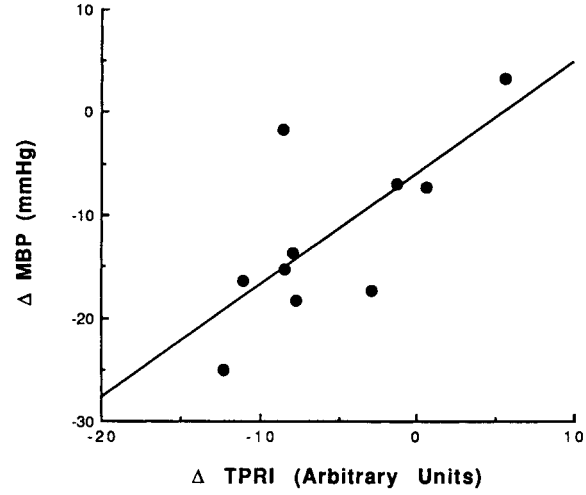

Fig. 2. Correlation between the differences in total peripheral resistance index (TPRI) and the differences in mean blood pressure (MBP) between treatment with quinapril versus placebo (r = 0.72, $p < 0.05$).

for quinapril (43.4 ± 2.0 arbitrary units) compared with placebo (48.8 ± 1.8 arbitrary units, $p < 0.01$). Although the small decrease in LVM in subjects receiving quinapril was not significant, wall stress was significantly decreased during quinapril treatment (Table II).

The differences in TPRI between the two treatments correlated significantly with the differences in MAP between the two treatments (Fig. 2).

Glomerular filtration rate and renal hemodynamics. GFR estimated by endogenous creatinine clearance remained statistically unchanged on quinapril compared with placebo (126 ± 9 versus 127 ± 10 ml/min per 1.73 m^2 body surface area, respectively).

PAH clearance averaged 521 ± 21 versus 519 ± 21 ml/min and hematocrit 42.6 ± 1.2 versus 42.1 ± 1.1 for subjects receiving quinapril and placebo, respectively (not significant). RBF was therefore statistically unchanged in subjects receiving quinapril (907 ± 36 ml/min) compared with placebo (896 ± 28 ml/min). The filtration fraction was also unchanged. RVR, however, was significantly ($p < 0.05$) lower in subjects receiving quinapril (12.2 ± 0.8 arbitrary units) compared with placebo (13.6 ± 0.6 arbitrary units), as shown in Fig. 3. The differences in RVR between the two treatments correlated with the differences in MAP between the two treatments (r = 0.63, p = 0.05). The change in RVR produced by quinapril was similar to the change in TPRI, and changes in the two resistance measurements were almost significantly correlated (r = 0.60, $p < 0.07$).

DISCUSSION

The present study showed that treatment of hypertensive subjects with quinapril, a novel nonsulfhydryl–ACE inhibitor, effectively lowers blood pressure at doses that do not cause notable side effects. The decrease in blood pressure in subjects receiving long-term quinapril therapy occurred without an increase in plasma catecholamines, reflex tachycardia, or cardiac output, and the decrease in blood pressure was associated with decreased total peripheral resistance. Renal blood flow and glomerular filtration rate were preserved, whereas renal vascular resistance showed a moderate decrease in patients receiving quinapril. Forearm blood flow and vascular resistance were unchanged

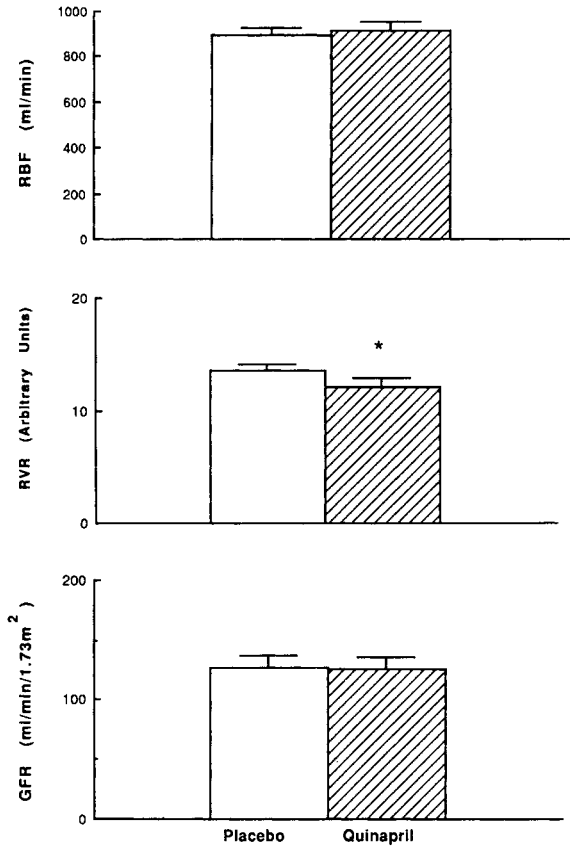

Fig. 3. Effects of quinapril on renal blood flow (RBF), renal vascular resistance (RVR), and glomerular filtration rate (GFR). Results are mean values + SE (n = 10). *Significantly different from placebo at $p < 0.05$.

in patients receiving quinapril compared with placebo.

Thus quinapril administered chronically lowers blood pressure by the same mechanism as other ACE inhibitors; that is, it induces a decrease in total and renal vascular resistance without changing cardiac output,[12-14,26-28] The changes induced by quinapril are at variance with the reduced cardiac output and unchanged total peripheral resistance observed on β-adrenergic blockade.[4] β-Blockade may worsen[4] the already depressed cardiac function[1-3] in hypertension. As opposed to β-blockade, vasodilation with, for example, an ACE inhibitor may reverse the established vascular changes in hypertension and may be preferable for the long-term treatment of hypertension.

The degree of counteracting reflex tachycardia and increase in cardiac output varies widely with vasodilator therapy of hypertension.[8-14] Even with a substantial decrease in blood pressure in patients receiving quinapril, heart rate, cardiac output and plasma catecholamines remained virtually unchanged. The same observation has been made for captopril[12,13,26-29] and enalapril[14,30] and lisinopril,[30] and it appears to be a class effect of ACE inhibition. It has been shown that with captopril,[31,32] enalapril,[33,34] and lisinopril,[34] the absence of reflex tachycardia with blood pressure reduction may be related to increased parasympathetic tone. It is likely that the absence of tachycardia with quinapril has a similar mechanism.

The reduction in systemic vascular resistance associated with chronic ACE inhibition appears to be unevenly distributed through the circulation. Lisinopril did not change the splanchnic vascular resistance,[35] and we did not detect a significant decrease in forearm vascular resistance in subjects receiving quinapril. However, captopril,[27,28,36,37] lisinopril[35] and, in the present study, quinapril, reduced renal vascular resistance. This may be explained by the particularly pronounced vasoconstricting action of angiotensin II in the renal circulation,[38,39] especially in patients with essential hypertension.[40]

Long-term treatment of essential hypertension with captopril or enalapril has been associated with no change[41,42] or with a relatively small increase[28,35,37] in renal blood flow and unchanged glomerular filtration rate.[28,35-37,41,42] An increase in renal blood flow may possibly be related to withdrawal of the effect of angiotensin, which is more potent in constricting the efferent than the afferent glomerular arteriole.[43] However, a decrease in filtration fraction may also indicate a redistribution of renal blood flow to more superficial nephrons known to have a low filtration fraction[44,45] or may relate to reduction in glomerular capillary hydraulic pressure.[46] In the present study, the decrease in blood pressure and renal vascular resistance was not accompanied by a change in renal plasma flow, glomerular filtration rate or filtration fraction. Presumably, the failure of renal blood flow to increase was attributable to reduction in perfusion pressure. Thus the antihypertensive effect of quinapril is not associated with compromise in autoregulation of renal hemodynamics. This conclusion is in agreement with studies in laboratory animals,[47] in which angiotensin II was not required for renal autoregulation.

The infusion rate of PAH used in the present study achieved a plasma PAH concentration in the middle of the range in which tubular secretion dominates excretion.[23] At this level, PAH clearance is independent of

plasma concentration and represents about 90% of renal plasma flow.[23] Therefore, use of PAH clearance may slightly underestimate true renal plasma flow. However, there is no reason to believe that quinapril per se influenced the renal extraction of PAH.

We found left ventricular peak systolic wall stress in the same range as reported by others.[48] Although we demonstrated a significant reduction in wall stress, which should promote regression of left ventricular hypertrophy, we did not find a significant reduction in LVM. It has been claimed that other ACE inhibitors decrease left ventricular mass.[49] However, a 4-week treatment period may be too short to detect regression of structural changes, and longer studies will be required to determine whether the trend toward lower LVM that we observed during quinapril therapy is indicative of regression.

After patients received 4 weeks of twice-daily quinapril therapy, further reductions in blood pressure were not observed during the 4-hour interval after quinapril dosing. This finding is interesting inasmuch as the plasma half-life of quinaprilat is approximately 2 hours and quinaprilat plasma concentrations are quite low 12 hours after a single 20 mg quinapril dose. These results suggest that stable blood pressure reduction can be achieved in patients with hypertension on chronic quinapril therapy, but the antihypertensive action of quinapril does not correlate well with quinaprilat pharmacokinetic parameters and may be more closely related to prolonged ACE inhibition or distant effect on tissue angiotensin II concentration.

In conclusion, we found that the antihypertensive effect of long-term quinapril therapy in patients with hypertension was associated with reduced total peripheral resistance and unchanged cardiac output. No reflex tachycardia or increase in plasma catecholamines was seen. Quinapril reduced renal vascular resistance but preserved renal blood flow and glomerular filtration rate. Forearm blood flow and resistance were unchanged.

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