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Arterial Hemodynamics in Human Hypertension

Effects of Angiotensin Converting Enzyme Inhibition

Chih-Tai Ting, Tsong-Ming Yang, Jaw-Wen Chen, Mau-Song Chang, Frank C.P. Yin

Previous studies have shown some distinct hemodynamic alterations in essential hypertension, including increased resistance, wave reflections, and pulse wave velocity and decreased systemic compliance. These abnormalities are completely normalized by nonspecific smooth muscle dilation with nitroprusside but not by combined α - and β -adrenergic blockade. The renin-angiotensin system, acting possibly via both circulating and local tissue effects, is thought to play an important role in essential hypertension, so its role in the altered hemodynamics deserves careful investigation. A hypertensive patient group was compared with a normotensive group similar in age, body size, and proportion of men and women. During diagnostic cardiac catheterization, ascending aortic micromanometer pressures and electromagnetic flows were measured in the baseline state. Intravenous captopril of a sufficient dosage (11 mg) to normalize blood pressure then was given to the hypertensive patients while measurements were repeated. From the pressures and flows, aortic input impedance, wave reflection magnitude, and compliance were computed. In the hypertensive group, the important hemodynamic alterations consisted of increased peripheral resistance, first zero crossing of aortic impedance phase angle, and wave reflections and decreased systemic compliance. Captopril had a pronounced hemodynamic effect. It normalized blood pressure, resistance, and impedance phase angle zero crossing. Compliance, although increased substantially by captopril, was still slightly lower than normotensive levels. The magnitude of wave reflections, although substantially lowered by angiotensin converting enzyme inhibition, was still persistently greater than normal. The present results, together with those previously reported, demonstrate that a complex interplay of factors underlies the increased smooth muscle tone in essential hypertension. Whereas nonspecific smooth muscle relaxation with nitroprusside is able to completely restore hemodynamics to a normal state, angiotensin converting enzyme inhibition alone, β -adrenergic blockade alone, or combined β - and α -blockade cannot do so. Therefore, if one wishes to completely normalize the hemodynamic alterations produced by hypertension in addition to treating the elevated blood pressure, one needs to appreciate the actions of these and other antihypertensive agents and select the appropriate combinations that will yield the desired results. (*Hypertension*. 1993;22:839-846.)

KEY WORDS • hypertension, essential • angiotensin converting enzyme inhibitors • captopril • compliance • hemodynamics

There are some distinct arterial hemodynamic alterations in humans with essential hypertension, including increased peripheral resistance, pulse wave velocity, and wave reflections^{1,3} and decreased systemic compliance.⁴⁻⁶ We previously reported that, compared with age-matched control subjects, these abnormalities in hypertensive patients are completely normalized during nonspecific smooth muscle vasodilation induced by nitroprusside,² indicating the important role of increased vascular smooth muscle tone in this disease state. However, the mechanism or mechanisms that underlie this increased smooth muscle tone are still

incompletely understood. Thus, we have been systematically investigating the effects of various classes of antihypertensive agents to see how each affects regional and global arterial hemodynamics. Short-term intravenous administration of the nonspecific β -blocker propranolol exacerbated some of the hypertensive hemodynamic abnormalities by further increasing both resistance and wave reflections.² The addition of α -adrenergic blockade in the presence of β -blockade essentially only counteracted the exacerbation caused by β -blockade.⁵ This suggests that there may be modulation of the increased aortic smooth muscle tone by β -adrenergically mediated vasodilation; loss of this vasodilation due to β -blockade cannot be overcome by the subsequent α -blockade. Additionally, in essential hypertension, there may be some non-adrenergically mediated smooth muscle vasoconstriction mediated by, for instance, the renin-angiotensin system.

Angiotensin II is a powerful vasoconstrictor.⁷ High circulating levels of this hormone are associated with hypertension in those people with the high-renin type of hypertension. Even in essential hypertensive patients

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with normal renin and angiotensin levels, however, angiotensin converting enzyme (ACE) inhibition is an effective antihypertensive therapy,^{8,9} suggesting a complex role of the renin-angiotensin system in modulating smooth muscle tone.¹⁰⁻¹² It has also recently been hypothesized that locally produced angiotensin, through paracrine or autocrine factors and independent of circulating levels, may affect smooth muscle tone and result in arterial hypertension.^{13,14} This possibility is supported by findings of elevated tissue angiotensin in animal models of hypertension,¹⁴⁻¹⁷ increased levels of plasma angiotensinogen in individuals with essential hypertension,¹⁸ and linkage between essential hypertension and the angiotensinogen gene.¹⁹ Thus, ACE inhibition may be efficacious in treating hypertension partly because of its circulating effects and partly because of some local action on tissue renin-angiotensin systems.

For all these reasons, we performed the present study to examine the extent to which ACE inhibition normalizes arterial hemodynamics in a group of patients with essential hypertension. Specifically, during cardiac catheterization, ascending aortic pressure and flow were measured, and aortic impedance, wave reflections, and compliance were calculated in a group of patients with essential hypertension during baseline conditions and after intravenous administration of sufficient captopril to normalize blood pressure. After administration of the drug, hemodynamics were compared with those in age-matched normotensive subjects in the baseline condition.

Methods

Patient Selection

The patient selection, data acquisition, and calculation methods are identical to those previously reported.^{2,5} Briefly, the study population consisted of ethnic Chinese who were undergoing diagnostic cardiac catheterization for chest pain syndrome, evaluation of a systolic murmur, or electrophysiological study for paroxysmal supraventricular tachycardia. The normotensive group was selected from subjects who had no prior history of nor symptoms related to hypertension. This group had normal physical examinations and multiple outpatient sphygmomanometric blood pressure measurements that were consistently in the normotensive range (systolic <140 and diastolic <90 mm Hg). The hypertensive group was selected from a population with recently diagnosed hypertension (persistent systolic and diastolic pressures >140 and >90, respectively, both during multiple outpatient examinations as well as after bed rest in the hospital). All patients either had not begun antihypertensive treatment or had medications stopped for at least 4 weeks before study. Secondary causes of hypertension were ruled out by the methods previously described.² All individuals gave informed consent for the investigative portion of the study according to the guidelines of the human investigation committee of the hospital.

Catheterization

All studies were performed after premedication with 5 mg IM chlorpheniramine maleate. Only those patients with no evidence of hemodynamically significant coro-

nary heart disease (<50% narrowing of any major coronary artery), congenital heart disease, or hemodynamically significant valvular heart disease were entered into the study. After completion of the diagnostic portion of the catheterization, high-fidelity micromanometer catheters (models VPC 673-D or SVPC 684D, Millar Instrument Co, Houston, Tex) were introduced via a femoral artery sheath into the aorta. These catheters had two micromanometers—one located at the tip and the other 5 to 7 cm from the tip of the catheter. In addition, an electromagnetic flow velocity sensor was located at or 3 cm from the second pressure sensor. The velocity sensor was connected to a flowmeter (model BL-613, Biotronex Laboratories, Kensington, Md). The flow system had a frequency response that was decreased by 3 dB at approximately 75 Hz. The catheter tip was advanced in a retrograde manner across the aortic valve to help stabilize the catheter and to keep the sensors in the center of the stream while allowing simultaneous measurement of left ventricular pressure and ascending aortic pressure and flow velocity. After placement across the valve, the catheter was manipulated to obtain an optimal flow velocity signal characterized by a steady diastolic level with maximal systolic amplitude and minimal late systolic negative flow.²⁰ To minimize drift, each catheter had been pre-soaked in saline for at least 2 hours before insertion. After the catheter was withdrawn at the completion of the study, the recordings with the pressure sensors barely submerged in the fluid at atmospheric pressure were used as the zero reference.

The pressure and flow velocity signals during each experimental condition were recorded on analog tape (No. 3968-A, Hewlett-Packard, Waltham, Mass) for later off-line analysis. Ascending aortic cross-sectional area during the baseline state was obtained from two-dimensional echocardiograms. Because previous studies in our laboratory demonstrated that the aortic cross-sectional area did not change by more than 0.2 cm² when blood pressures were altered over a similar range as encountered in the present study,² the initial aortic area was used throughout the remainder of the study to convert flow velocity to volume flow.

Protocol

Baseline hemodynamics were first recorded in each group. In the hypertensive group, intravenous captopril was then administered using a modification of a previously reported method²¹: 2 mg was administered over 1 minute, and hemodynamic recordings were made 10 minutes later. If either systolic or diastolic blood pressure was still elevated above 140/90 mm Hg, another 4 mg was administered over 1 minute, and the data were recorded after another 10 minutes. If either pressure was still above normal, another 8 mg was given over 1 minute, and the data recorded 15 minutes later. The average maximum dose was 11 mg (range, 6 to 14 mg). The data reported here are those at the time of the lowest blood pressure achieved in each patient. The pressure was still elevated at the end of the third dose in only one patient. We elected not to administer more drug to this patient and included his data in the group average.

Calculations and Data Analysis

The analog records were digitized at a rate of 250 Hz using a 12-bit analog-to-digital convertor (Tekmar Labmaster, Tekmar Co, Solon, Ohio) interfaced to an IBM microcomputer. The digitized signals were analyzed with the use of custom software written in our laboratory. The digitized flow velocity signals were displayed on the monitor, and only beats that had no significant baseline drift and no significant negative dip or secondary rise in diastole were considered acceptable for analysis.² Zero flow was assumed to be that in late diastole. The calibration of the flow velocity probe was performed in all patients by the Fick method using a nomogram for assumed resting oxygen consumption based on the subject's age, body weight, sex, heart rate, and hemoglobin concentration. From the digitized flow velocity signal we determined a time-averaged flow velocity for at least 15 separate beats. This mean velocity was converted to volume flow by multiplying by the resting aortic cross-sectional area. The appropriate calibration factor for each probe was then determined by matching the cardiac outputs obtained from the Fick method with the mean output calculated from the digitized flow signals.

For each acceptable beat the noise level of the flow signal was first determined by performing Fourier analysis on the diastolic portion of the flow signal. The harmonic with the largest modulus was considered to represent the noise. The pressure and flow signals were then resolved into their Fourier harmonics. Only flow harmonics with moduli greater than twice the maximum noise level were included in the subsequent calculations.²⁰ The input impedance modulus and phase angle for each harmonic above the noise level were calculated as the ratio of the pressure and flow moduli and the difference of the pressure and flow phase angles, respectively. We had previously determined that the combined flow-sensor flowmeter system had a phase lag of 1.3° per hertz, which was accounted for in subsequent calculations. The characteristic impedance was estimated by averaging the suitable impedance moduli for frequencies of 4 Hz and higher.²⁰ Total external power, consisting of both pressure and kinetic terms for the left ventricle, was calculated as previously reported.²⁰ The oscillatory power, the steady power, and the ratio of oscillatory to total power, indicating the efficiency with which the pulsatile energy was converted into forward flow, were also calculated. The frequency of the first zero crossing of the impedance phase angle was determined by linear interpolation from the phase angle data. Finally, we decomposed the pressure wave into its forward and backward components as described previously.^{2,22,23} The ratio of the backward to forward wave components was used to characterize the degree of arterial wave reflection reaching the aortic root. We have previously shown that the reflection characteristics of the arterial tree can be adequately described by this manner, which is easier to analyze and compare than the more complete but cumbersome reflection spectrum.²⁴

We also calculated the overall arterial compliance using our previously proposed method which assumes that the vasculature can be modeled by a Windkessel

without having to assume a monoexponential decay of the diastolic aortic pressure wave.²⁵ The method explicitly accounts for the pressure dependence of compliance by assuming a specific value for the exponential coefficients of a nonlinear pressure-volume relation. For the present study we assumed a value of -0.01 for this coefficient for all groups under all conditions. Assuming a three-element Windkessel model of the vasculature,²⁶ the expression for the compliance at any pressure is²⁷

$$C = \frac{b \times SV \times e^{bP}}{\left(\frac{A_s + A_d}{A_d} - Z_c \times \frac{SV}{A_d} \right) (e^{bP_s} - e^{bP_d})}$$

where P_s and P_d are the pressures at end systole and end diastole, A_s and A_d are the areas under the systolic and diastolic portions of the pressure waveform, SV is stroke volume, Z_c is characteristic impedance, and b is the nonlinear coefficient.

The above hemodynamic parameters were obtained for each beat. In our experience, the coefficients of variation for the directly measured parameters of heart rate, pressure, and flow are approximately 5%, 2%, and 5% to 10%, respectively. For derived parameters, the coefficients of variation for resistance and Z_c , power, wave reflection, and compliance are 15% to 20%. Therefore, the data from at least a minimum of five (mean, 11.7; range, five to 26) acceptable beats were averaged to obtain what we consider to be representative findings for each individual for each condition.

Statistical Analysis

The age and morphometric and baseline hemodynamic data for the normotensive and hypertensive groups were compared using unpaired t tests. In the hypertensive group, the effect of captopril on the hemodynamic data was assessed using a paired t test, and the results after the drug were compared with the baseline normotensive data using unpaired t tests. For completeness, all values of $P < .10$ are listed, although statistical significance was considered to be at a value of $P = .05$.

Results

The normotensive group was composed of 14 subjects (10 men, 4 women). The data for 10 of the normotensive subjects were reported in our previous study.⁵ The hypertensive group consisted of 12 patients with a similar sex distribution as the normotensive group (9 men, 3 women). The normotensive and hypertensive groups did not differ significantly in age (32.6 ± 7.4 versus 37.0 ± 4.8 years), height (167.2 ± 9.0 versus 163.5 ± 8.3 cm), or body weight (66.7 ± 12.4 versus 67.6 ± 9.1 kg) but did have different aortic cross-sectional areas (6.02 ± 1.36 versus 7.43 ± 1.51 cm², $P < .05$).

The averaged aortic impedance modulus and phase angle spectra for the normotensive and hypertensive groups during baseline conditions and for the hypertensive group after captopril are shown in Fig 1. To show the frequency-dependent nature of the impedance and yet account for heart rate variability among the individuals in a group, the data are grouped into 1-Hz frequency intervals. For clarity, only the mean data for each group are shown. During baseline conditions, the modulus spectrum of the hypertensive group is shifted

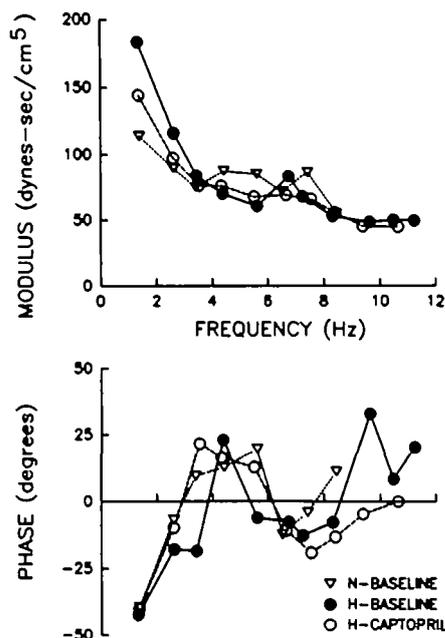


FIG 1. Line graphs show averaged baseline impedance moduli and phase spectra for normotensive group (N) (∇) and hypertensive group (H) (\bullet) and for hypertensive group after intravenous captopril (\circ). Data are grouped in 1-Hz frequency intervals for convenience. Because there are differences in heart rate within each group, different harmonics may be represented in some frequency intervals.

so that the lower-frequency (<4 Hz) moduli of the group are elevated above normotensive values. The phase angle spectrum of the hypertensive compared with the normotensive group is shifted upward and rightward so the frequency of the first zero crossing is higher than in the normotensive group. After captopril administration, the low-frequency portion of the modulus spectrum of the hypertensive group is shifted toward that of the normotensive group, but the differences between groups are not completely eliminated. The phase angle spectrum, however, is shifted so that the difference in the first zero crossing between groups is eliminated.

Fig 2 illustrates representative ascending aortic pressure waveforms along with their forward and backward components for a normotensive subject and hypertensive patient in the baseline state as well as after captopril in the hypertensive patient. Compared with the normotensive case, the late systolic peak of pressure indicative of a large reflected wave is evident in the hypertensive waveform. The larger magnitude of this reflected wave in the hypertensive than the normotensive case is more clearly seen in the backward wave component (Fig 2, right bottom panel). After captopril the reflected wave is somewhat reduced in the hypertensive patient but still not to the level seen in the normotensive subject.

The detailed hemodynamic data for the two groups are summarized in the Table. Comparing the two groups during baseline conditions shows that the hypertensive patients had higher central aortic systolic, diastolic, and mean pressures; peripheral resistance; left ventricular end-diastolic pressure; total external power;

zero crossing of impedance phase; and forward pressure wave component and a much higher backward pressure wave component, resulting in a larger wave reflection index. The characteristic impedance of the hypertensive group was slightly lower than that of the normotensive group. The compliances at all pressures, as well as that extrapolated to zero pressure, were lower in the hypertensive group. Comparing the compliances at a nearly equivalent pressure, namely, at the mean aortic pressure in the normotensive subjects and diastolic pressure in the hypertensive patients, still revealed a significantly lower compliance in the hypertensive group.

Captopril produced a significant hemodynamic effect as evidenced by significant decreases in aortic pressures, resistance, external power, left ventricular end-diastolic pressure, and both the forward and backward wave components as well as the wave reflection index. In addition, all compliances increased significantly. Comparing these data with the baseline normotensive values revealed no difference in resistance or zero crossing of phase angle but persistently higher blood pressures (but now within the normotensive range), higher external power, greater wave reflection index, and nearly normalized aortic compliances at all pressures.

Discussion

The hemodynamic alterations in this group of hypertensive patients were the same as reported in our previous studies.^{2,4,5} In particular, the baseline wave reflections were higher and arterial compliance was lower than in the normotensive control subjects. Our method of estimating compliance allows for comparisons at different pressures, so we can estimate compliances in both groups at matched pressures. Because the hypertensive compliances are lower even at matched blood pressures, this is evidence that the decreased compliance is not a purely passive effect of the elevated blood pressure.^{2,4,28}

In the baseline hypertensive state, there is a late systolic peak in the central aortic pressure waveform that is not seen in the normotensive subjects (Fig 2). The late systolic pressure peak has been associated with aging and other circumstances that modify wave reflections.^{29,30} The peak is due to the combination of increased wave reflection together with a more proximal predominant reflecting site and/or higher pulse wave velocity. In aging, these changes are due to increased arterial stiffness arising from structural changes in the wall rather than increased smooth muscle tone as in hypertension. From the data reported in the present study, however, it is difficult to differentiate between a more proximal reflection site and increased pulse wave velocity because the frequency of the first zero crossing of the impedance phase angle is affected by both reflection site and pulse wave velocity. Because the body heights of the two groups were not statistically different (see "Results"), a more proximal reflecting site solely due to body size differences is unlikely. Moreover, our direct measurements of regional pulse wave velocities in similar groups of normotensive subjects and hypertensive patients demonstrated a markedly increased pulse wave velocity in the hypertensive patients with no evidence for a more central site of reflections.¹ Finally, because pulse wave velocity, arte-

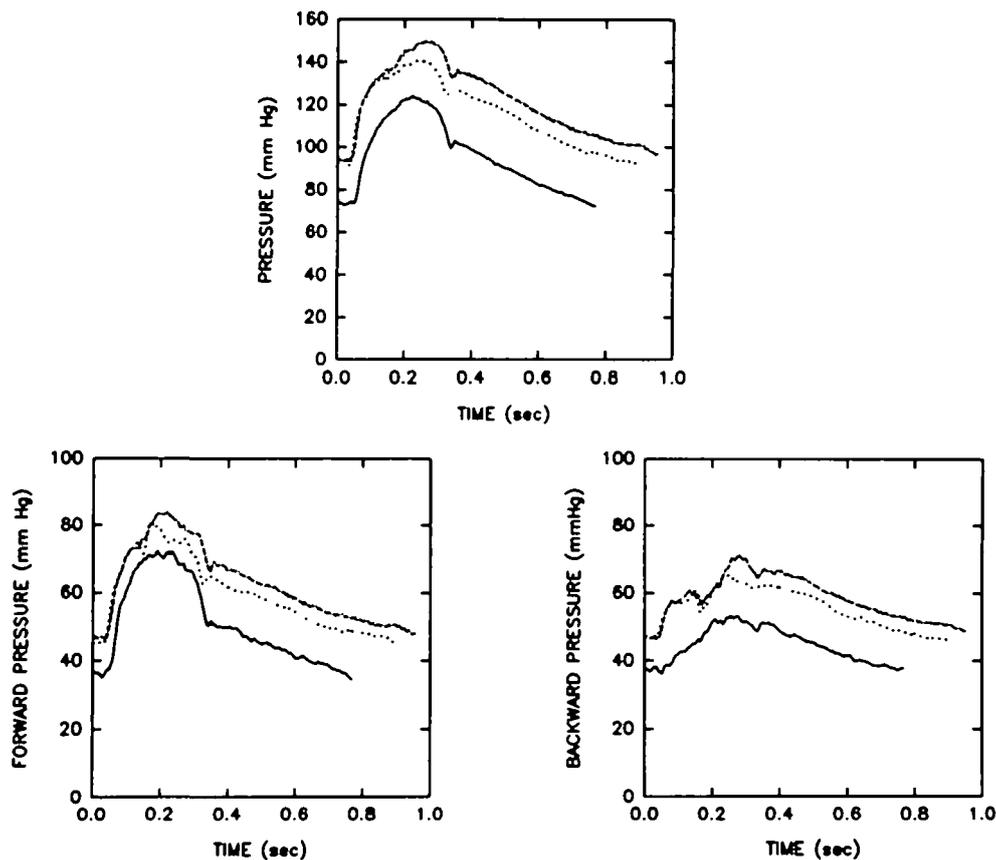


FIG 2. Plots show ascending aorta pressure waveforms (top) along with their forward (bottom left) and backward (bottom right) components in a representative normotensive and hypertensive patient. Solid line depicts the normotensive baseline; dashed line is hypertensive baseline; dotted line is the hypertensive response after captopril infusion. Comparison of baseline states shows much higher backward wave and prominent late systolic peak in the hypertensive patient, both of which are somewhat attenuated after angiotensin converting enzyme inhibition.

rial stiffness, and blood pressure are all directly related, it is reasonable to ascribe a decrease in pulse wave velocity to the fall in blood pressure after ACE inhibition. It is more difficult to envision how ACE inhibition would move a reflecting site more proximally in the arterial system, although we cannot exclude this possibility.

Regardless of the mechanism for the elevated late systolic pressure peak, because it occurs during systole, it represents an additional hemodynamic load on the ejecting left ventricle that is not present in young normotensive subjects in whom the low pulse wave velocity causes the reflection to be manifest in diastole. It may be that this increased load contributes to the deleterious results of hypertension on the heart. Because ACE inhibition apparently only partially corrects this elevated reflection, an additional load remains on the heart. The long-term effects of this partial normalization need to be determined.

Our results demonstrate that, although captopril has a clear effect on hypertensive hemodynamics, used alone it is not able to completely normalize hemodynamics. Specifically, whereas blood pressure was lowered into the normotensive range and compliance was nearly normalized, ACE inhibition could not completely normalize the elevated wave reflections. Recent evi-

dence suggests that ACE inhibition has a major direct dilating effect on large arteries.^{13,31-36} Therefore, it is not too surprising that captopril affects both compliance and wave reflection. What was unexpected, however, was that captopril more nearly normalized arterial compliance than wave reflections. One must remember that, although these hemodynamic responses represent the net effect seen at the entrance to the systemic bed, they could be manifestations of different regions of the aorta and arterial system. Although our method of estimating compliance does not tell us where in the bed most of the compliance is located, there is in fact some evidence that much of the arterial compliance resides in the very proximal portion of the aortic root.³⁷ In contrast, there undoubtedly are diffuse reflections arising from the entire arterial system including the periphery,³⁸ even though there appears to be a major site of wave reflections in both normotensive subjects and hypertensive patients at or near the renal arteries.^{1,39} In view of all of these findings, it should not be too surprising that the compliance and wave reflections might be affected differently by an agent such as captopril. Although the blood pressures after captopril in the hypertensive group were in the normal range, they were still somewhat elevated above the values in the normotensive group. One might argue that giving higher

Hemodynamics in Normotensive and Hypertensive Patients Under Baseline Conditions and in Hypertensive Patients After Captopril Administration

Parameter	Normotensive Baseline	Hypertensive (n=12)			
		Baseline	P*	Captopril	P*
Heart rate, bpm	83.5±13.5	79.7±8.9	NS	81.7±12.7	NS
Stroke volume, mL	74.9±15.0	80.2±13.2	NS	82.4±17.4	NS
Blood pressure, mm Hg					
Aortic systolic (P _s)	111.8±11.3	156.9±16.9	.001	137.4±14.2†	.001
Aortic diastolic (P _d)	73.5±9.9	96.2±6.1	.001	87.0±5.1†	.001
Mean (P _m)	92.0±10.1	123.5±8.9	.001	110.6±7.8†	.001
Resistance, dyne · s/cm ⁵	1239±224	1612±326	.002	1403±374†	NS
Z _c , dyne · s/cm ⁵	75.5±21.5	60.4±10.0	.04	62.3±12.3	.07
External power, mW					
Total (W _t)	1497±347	2055±236	.001	1925±328‡	.004
Ratio (W _o /W _t)	0.15±0.03	0.15±0.02	NS	0.15±0.02	NS
EDP, mm Hg	10.2±4.1	16.1±8.1	.03	11.8±8.1‡	NS
Pressure wave components, mm Hg					
Forward (P _f)	31.9±3.8	40.1±5.5	.001	37.0±4.9‡	.007
Backward (P _b)	13.7±2.5	25.0±6.3	.001	19.3±5.3†	.002
P _b /P _f	0.43±0.07	0.62±0.09	.001	0.52±0.09†	.01
f ₀ , Hz	3.1±0.6	3.9±1.1	.03	3.5±1.2	NS
Compliances, mL/mm Hg					
Zero pressure (C ₀)	5.50±2.16	4.08±1.11	.05	4.83±1.8‡	NS
Systolic (C _s)	1.81±0.78	0.89±0.34	.001	1.27±0.62†	.07
Diastolic (C _d)	2.53±0.97	1.53±0.44	.003	1.97±0.80‡	NS
Mean (C _m)	2.15±0.84	1.20±0.38	.001	1.63±0.70†	.10

bpm indicates beats per minute; Z_c, characteristic impedance; EDP, left ventricular end-diastolic pressure; and f₀, first zero crossing of impedance phase angle.

*Versus normotensive baseline.

†P<.005, ‡P<.05 vs hypertensive baseline by paired t test.

doses of captopril might have further lowered the pressure and resulted in complete normalization of the hemodynamic alterations. We do not think this is likely for the following reasons. First, our previous results have shown that there is not a direct relation between the level of blood pressure and the amount of wave reflections. For example, with large increases in blood pressure induced by handgrip exercise in normotensive subjects, the amount of wave reflection was not greatly increased.² Moreover, in hypertensive patients given nitroprusside the wave reflections were normalized even though the blood pressures after nitroprusside were still higher than in the normotensive subjects. Another study showed that the same percentage increase in arterial compliance was achieved despite different levels of blood pressure reduction with either short- or long-term captopril administration.³⁵ Another study showed that higher doses of ACE inhibitors tend to preferentially increase large artery compliance without having an additional hypotensive effect.⁴⁰ Several other studies have also shown that there is a maximum blood pressure-lowering effect of orally administered captopril of approximately 15% to 25%.^{8,40} Although there are no other comparable data on intravenously administered

captopril in hypertensive patients, our results tend to support this notion that the amount of vasodilation achievable by ACE inhibition is limited.

From data such as those in the present study, one obviously cannot ascertain the mechanism of action of captopril. There are several possible mechanisms for these hemodynamic effects of captopril. Other than the direct vasodilator properties mentioned above, captopril could potentially act to lower local tissue levels of angiotensin II, thereby resulting in less local vasoconstriction. Moreover, there could be other secondary local effects of ACE inhibition, such as removal of the facilitatory vasoconstrictive effects of angiotensin, increasing bradykinin or prostaglandin levels, etc.^{8,10,12,41,42} that would also result in some degree of vasodilation. Regardless of the mechanisms of captopril, our data indicate that short-term ACE inhibition alone is not sufficient to produce enough vasodilation or sufficient vasodilation at the appropriate sites to completely normalize the abnormal hemodynamics, particularly the elevated wave reflections, of essential hypertension.

Some limitations of our study deserve discussion. Our method of estimating total arterial compliance, although having certain advantages over other methods,

particularly the ability to account for the pressure dependence of compliance, also has limitations. First, it is based on a Windkessel model of the vasculature, which implies no wave reflections. Our other hemodynamic data, however, clearly indicate that excess wave reflections are present in the hypertensive vasculature. Thus, interpretations of the compliance data must be made keeping this model limitation in mind. Accounting for the pressure dependence requires that one assume a value for the exponential coefficient, b . In this study we assumed a nominal value of -0.01 for both groups in the baseline state and after captopril in the hypertensive patients. We have shown⁴ that severe vasoconstriction will increase b to -0.005 , and severe vasodilation will decrease it to -0.015 . Using identical data, assuming these values of b will yield slightly lower or higher estimates of compliance, respectively. Thus, by selecting the same value for b in all conditions, we have if anything underestimated the differences in compliance between the groups in the baseline state. In addition, by assuming an unchanged value for b in the hypertensive patients after captopril, we are underestimating the increase in compliance due to the vasodilator actions of the drug. Thus, had we estimated compliance using a value of b representing more vasodilation, our conclusion that captopril nearly normalizes the abnormally low compliances would be even more firm.

Our results and conclusions pertain only to the short-term effects of the drug. Although we cannot predict what the long-term responses would be, the fact that there were short-term changes indicates that there were significant and major effects of the drug. Additionally, whether these short-term effects reflect what is happening in either the circulating or tissue renin-angiotensin systems cannot be addressed by our data. Moreover, aside from the pressure-dependent compliance effects, we cannot ascertain if there is a direct effect of the drug on other hemodynamic parameters, eg, wave reflections, in the absence of a fall in blood pressure, because we found a decrease in blood pressure, albeit not into the normotensive range, coupled with a fall in wave reflection even after the first 2-mg dose of the drug.

Finally, because of the difficulties of identifying suitable subjects for invasive studies such as this, our normotensive data were obtained over a longer time period than the hypertensive group. However, because the data that we obtained in several different hypertensive groups over the same time span are indistinguishable^{2,4,5} and because all the data have been obtained in the same laboratory with the same essential personnel, we doubt that the differences between normotensive subjects and hypertensive patients can be attributed to anomalies in the normotensive group.

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