Arterial Hemodynamics in Human Hypertension
Effects of Adrenergic Blockade

C.T. Ting, MD; C.Y. Chou, MD; M.S. Chang, MD; S.P. Wang, MD;
B.N. Chiang, MD; and Frank C.P. Yin, MD, PhD

Background. Resistance, pulse wave velocity, and wave reflections have been shown to be increased in patients with essential hypertension compared with normotensive controls. These alterations are completely normalized by nitroprusside infusion but exacerbated during \( \beta \)-adrenergic blockade, suggesting an enhanced smooth muscle tone that is in part modulated by adrenergically mediated vasodilation. The present study was performed to examine the extent to which this apparently enhanced smooth muscle tone is a result of \( \alpha \)-adrenergically mediated vasoconstriction.

Methods and Results. Age-matched normotensive and hypertensive Chinese subjects were instrumented with catheter-tipped micromanometers and an electromagnetic flow velocity sensor positioned in the ascending aorta. Aortic impedance and wave reflection properties were obtained from Fourier analysis of the pressure and flow signals during baseline conditions, after \( \beta \)-blockade with propranolol (0.15 mg/kg i.v.), and after \( \alpha \)-blockade with intravenous phentolamine (range, 15–80 mg) that was sufficient to either normalize blood pressure or produce a pressure that could not be further lowered. Compared with normotensives, in the baseline state, hypertensives had elevated resistance (1,962 versus 1,268 dyne·sec/cm\(^2\), \( p<0.001 \)), total power (1,893 versus 1,568 mW, \( p<0.08 \)), reflected pressure wave component (25.6 versus 13.5 mm Hg, \( p<0.001 \)), ratio of reflected to forward wave (0.65 versus 0.42, \( p<0.001 \)), and pulse wave velocity as determined from the frequency of the first zero-crossing of impedance phase angle (4.6 versus 3.5 Hz, \( p<0.03 \)). During combined \( \alpha \)- and \( \beta \)-adrenergic blockade, blood pressure decreased into the normal range (from 162/103 to 131/87 mm Hg) but was still somewhat higher than that in the normotensive subjects. Resistance (1,914 dyne·sec/cm\(^2\), \( p<0.03 \)), reflected wave (19.5 mm Hg, \( p<0.01 \)), and ratio of reflected to forward wave (0.61, \( p<0.001 \)) were, however, persistently elevated above normal values.

Conclusions. \( \alpha \)-Adrenergically mediated vasoconstriction cannot account for all of the hemodynamic alterations seen in essential hypertension. (Circulation 1991;84:1049–1057)

Recent reports have demonstrated distinct alterations in arterial hemodynamics in patients with essential hypertension compared with normal subjects. In a comparison of young, age-matched normotensive subjects with hypertensive patients, we found higher peripheral resistance, characteristic impedance, total external power, wave reflections, and pulse wave velocity and lower compliance in the hypertensives. All of these abnormalities were completely normalized during the administration of nitroprusside. Furthermore, when \( \beta \)-adrenergic blockade was produced with intravenous propranolol, the already abnormally high resistance and magnitude of wave reflections were further increased. These findings suggested that the hemodynamic alterations associated with essential hypertension were related to an elevated level of smooth muscle tone that was modulated in the baseline state by \( \beta \)-adrenergically mediated vasodilation.

Enhanced postsynaptic \( \alpha \)-adrenergically mediated vasoconstriction is a widely accepted accompaniment of essential hypertension. Although there are many studies documenting the lowering of resistance and blood pressure by peripheral \( \alpha \)-adrenergic antagonists or central \( \alpha \)-adrenergic agonists there are no studies that have examined the effect of...
α-blockade on arterial impedance and wave reflection in hypertensives. Thus, the present study was undertaken to examine the extent to which α-adrenergically mediated vasoconstriction contributes to the altered hemodynamics of essential hypertension. Specifically, we examined whether acute, non-specific, peripheral α-adrenergic blockade (to a degree that normalized blood pressure) would produce results similar to those of nonspecific smooth muscle vasodilation. During cardiac catheterization, ascending aortic pressure and flow were recorded in a group of young patients with essential hypertension during baseline conditions, during acute β-adrenergic blockade with intravenous propranolol, and then during combined blockade with intravenous propranolol and phentolamine. Aortic input impedance and wave reflection properties for each condition were compared with those in age-matched, normotensive subjects under baseline conditions and after acute β-blockade.

**Methods**

**Patient Selection**

Patient selection, data acquisition, and calculation methods are identical to those previously reported. Briefly, candidates for the study were 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 patients who had no prior history of or symptoms related to hypertension. This group had normal physical examinations and multiple outpatient syphgmomanometric blood pressure measurements that were consistently within the normal range (systolic, less than 140 mm Hg; diastolic, less than 90 mm Hg). The hypertensive group was selected from a population with recently diagnosed hypertension (persistent systolic and diastolic pressures of more than 140 and 90 mm Hg, respectively, during multiple outpatient examinations as well as after bedrest in the hospital). Secondary causes of hypertension were ruled out by the methods previously described. All subjects gave informed consent for the investigative portion of the study according to the guidelines of the hospital's human investigation committee.

**Catheterization**

All studies were performed after premedication with 5 mg i.m. chlorpheniramine maleate. Only patients with no evidence of hemodynamically significant coronary heart disease (less than 50% narrowing of any major coronary artery), congenital heart disease, or hemodynamically significant valvular heart disease were entered into the study. Commercially available high-fidelity micromanometer catheters (model VPC 673-D or SVPC 684D, Millar Instruments Co., Houston) were introduced via a femoral artery sheath into the aorta. These catheters had two micromanometers—one located at the tip, and the other located 5–7 cm from the tip. In addition, there was an electromagnetic flow velocity sensor 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 about 75 Hz. The catheter tip was advanced retrograde across the aortic valve to help stabilize the catheter and to keep the sensors in the center of the stream while allowing simultaneous measurements 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. To minimize drift, each catheter had been presoaked in saline for at least 2 hours before insertion. After withdrawing the catheter at the completion of the study, the pressure with the pressure sensor barely submerged in the fluid at atmospheric pressure was used as the zero reference.

The pressure and flow velocity signals during each experimental condition were recorded on analog tape (model 3968-A, Hewlett-Packard, Waltham, Mass.) for later off-line analysis. An estimation of 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 in the present study, the initial aortic area was used throughout the remainder of the study to convert flow velocity to volume flow.

**Protocol**

Baseline, resting hemodynamics were first recorded in both groups. To eliminate possible β-adrenergically mediated peripheral vasodilation and/or inotropic or chronotropic effects, we administered propranolol to both groups at a rate of 1 mg/min until a dose of 0.15 mg/kg had been delivered. Hemodynamic measurements were repeated immediately on completion of β-blockade. Finally, acute α-blockade combined with β-blockade in the hypertensive group was produced by the administration of intravenous phentolamine beginning with a dose of 1 mg/min. The dose was increased by 1 mg/min every 3 minutes until both systolic and diastolic blood pressures decreased to normal levels. In those instances in which the pressures could not be completely lowered into the normal range, the dose was increased until the patient began to experience distinct side effects such as nausea, abdominal cramps, or dizziness. At these end points, the infusion was maintained while pressure and flow were recorded. After stopping the infusion, recordings were made for an additional 3–5 minutes. The combined α- and β-blockade data reported herein
are those at the lowest blood pressure achieved during recording.

Calculations and Data Analysis

The analog records were digitized at a rate of 250 Hz using a 12-bit analog-to-digital converter (Teckmar Labmaster, Solon, Ohio) interfaced to an IBM/AT microcomputer. The digitized signals were analyzed using 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. Zero flow was assumed to be that in late diastole. The calibration of the flow velocity probe was performed in all of the 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 it 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 outputs calculated from the digitized flow signals.

For each condition, the data from a minimum of six (range, six to 28; average, 12) acceptable beats were averaged. 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 more than twice the maximum noise level were included in the subsequent calculations. 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°/Hz, which was accounted for in subsequent calculations. The characteristic impedance (Zc) was estimated by averaging the suitable impedance moduli for frequencies of 4 Hz and higher. Total external power, consisting of both pressure and kinetic terms for the left ventricle, was calculated as previously reported. The oscillatory power, steady power, and ratio of oscillatory to total power, indicating the efficiency with which the pulsatile energy was converted into forward flow, were also calculated. Pulse wave velocity was estimated by determining the frequency of the first zero-crossing of the impedance phase angle by linear extrapolation from the phase data. Finally, we decomposed the pressure wave into its forward and backward components as described previously.

The magnitudes (pulse pressure) of the forward and backward components along with the ratio of the backward to the forward magnitude were used to characterize the wave reflection properties. We have previously shown that the reflection characteristics of the arterial tree can be adequately described in this manner, which is easier to analyze and compare than the more complete but cumbersome reflection spectrum.

Statistical Analysis

In the hypertensive group, the effect of the two drugs was assessed using repeated measures analysis of variance with the Bonferroni correction applied for multiple comparisons using the pooled mean squared error. The specific effect of β-blockade was assessed in each group by paired analysis. Unpaired t tests were used to compare the baseline values between the two groups, to compare the responses to β-blockade in each group, and to compare the baseline normotensive data with those after combined α- and β-blockade in the hypertensive group. Statistical significance was considered to be a probability level of 0.05.

Results

The study group comprised 10 normotensive and 12 hypertensive patients who had acceptable data for all of the protocols. Some pertinent clinical data for the groups are summarized in Table 1. Both groups contained members of each sex, although there were more men in each group. The groups did not differ in age, body size, or baseline cross-sectional area of the aortic root.

The averaged impedance modulus and phase spectra for the normotensive group during baseline conditions and β-blockade are shown in Figure 1. The spectra for the hypertensive group during baseline conditions, β-blockade, and combined β- and α-blockade are shown in Figure 2. For ease of comparison, only the mean data grouped into 1-Hz frequency intervals are shown. Compared with the normotensives, the hypertensives have a baseline modulus spectrum that is shifted upward at all frequencies and a phase angle spectrum that is shifted to higher frequencies. β-Blockade markedly increased resistance and caused a slight rightward shift of the lower-frequency phase angle spectrum. The relatively greater effect of β-blockade in the hypertensives compared with the normotensives is evident. The pronounced effect of combined blockade in the hypertensives in both the modulus and phase spectra is also clearly seen. Combined β- and α-blockade lowered resistance to the baseline value and produced a distinct leftward shift of the phase spectrum, but the impedance spectra still did not match those of the normotensives. All of the hemodynamic data for the two groups are summarized in Table 2. In the baseline state, the hypertensive group had significantly higher resistance, external power, wave reflection, and pulse wave velocity than the normotensive group. The groups did not differ in heart rate, stroke volume, left ventricular end-diastolic pressure
(LVEDP), characteristic impedance, or percent of oscillatory power.

In both groups, β-blockade lowered both heart rate and total external power and increased resistance, LVEDP, and the backward pressure wave component. There were some significantly different responses to β-blockade, however, between the two groups. The increases in resistance and backward wave component were much larger in the hypertensive than in the normotensive group. This, coupled with increases in both the forward wave and characteristic impedance in the hypertensive group and decreases in the normotensive group, resulted in a significant increase in peak systolic pressure as well as the ratio of backward pressure to forward pressure in the hypertensive but not the normotensive group. β-Blockade had no effect in either group on pulse wave velocity or the percentage of oscillatory power.

In the hypertensive group, although combined adrenergic blockade decreased the systolic, diastolic, and mean blood pressures into normal ranges, each was still statistically higher than the respective baseline normotensive value. Furthermore, despite the normalization of pressures, resistance, backward wave component, and ratio of backward to forward components remained significantly elevated above baseline normotensive values.

The implications of these hemodynamic responses, particularly the effect of reflections, can be visualized in another manner by examining the aortic pressure waveform with its forward and backward components. Representative tracings for a normotensive and a hypertensive patient in the baseline state are shown in Figure 3. The primary difference between the two is the larger absolute value and pulse pressure of the backward wave in the hypertensive patient. The arrival of this reflected wave late in systole contributes significantly to the elevation of peak systolic blood pressure. The effects of the drug interventions for the normotensive and hypertensive patients are shown in

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<th>Weight (kg)</th>
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<th>Blood pressure Baseline (mm Hg)</th>
<th>Ind + Ph (mm Hg)</th>
<th>Phentolamine infusion (mg)</th>
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CSA, cross-sectional area; Ind, propranolol; Ph, phentolamine.
Figures 4 and 5, respectively. β-Blockade had minimal effect on the backward wave component in the normotensive patient, whereas there was a significant increase in reflection in the hypertensive patient. In fact, in this patient, the timing of the reflected wave was such that the peak systolic pressure was broadened and the early diastolic portion was rendered concave downward rather than being almost straight. Even after combined α- and β-blockade when blood pressure was decreased into the normal range, there was still a prominent reflected wave.

Discussion

Results of the present study generally confirm our previous findings that compared with age-matched controls, alterations in baseline hemodynamic parameters associated with essential hypertension consist of decreased compliance, increased pulse wave velocity, and increased wave reflection—the latter of which is further exacerbated by acute β-blockade. Unlike our previous results, however, we did not find a greater characteristic impedance in the hypertensive group. This is not altogether surprising because it is well known that characteristic impedance is difficult to accurately assess.18

New findings of this study are the directionally different responses of characteristic impedance and forward wave components in the two groups as well as the larger increase in resistance and wave reflection in the hypertensive compared with the normotensive group during β-blockade. The latter suggests a greater extent of modulation of the elevated smooth muscle tone in hypertensives by β-adrenergically mediated vasodilation. This increase in resistance in hypertensives after acute β-blockade has been reported previously.25–28 In contrast to hypertensives, although the normotensive group also appears to have some modulation, it does not appear to be hemodynamically significant. These data, however, cannot address the issue of whether there is an alteration in intrinsic vascular sympathetic reactivity in essential hypertension for which the evidence is conflicting.7,29,30

The major new finding was the persistently elevated resistance and wave reflections in the hypertensive group despite normalization of blood pressure after combined adrenergic blockade. Although combined blockade reduced the magnitude of the reflected wave, it remained well above normal values. It may be the presence of this relatively large reflected wave that is responsible for the inability to further lower blood pressure, despite large doses of phentolamine, in many of the hypertensive subjects. Furthermore, over the lifetime of the patient, this
TABLE 2. Summary of Hemodynamics in Normotensive Subjects and Hypertensive Patients

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<td>1,565*</td>
<td>0.13</td>
<td>16.1*</td>
<td>41.2**</td>
<td>29.8**</td>
<td>0.73*</td>
</tr>
<tr>
<td>Pr + Ph</td>
<td>6.6</td>
<td>22.7</td>
<td>20.1†</td>
<td>7.9</td>
<td>11.0</td>
<td>978</td>
<td>19.7</td>
<td>542</td>
<td>0.02</td>
<td>7.0</td>
<td>8.0</td>
<td>6.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Pr + Ph + Ph</td>
<td>8.3</td>
<td>25.3</td>
<td>12.8</td>
<td>8.9</td>
<td>9.5</td>
<td>796</td>
<td>22.5</td>
<td>519</td>
<td>0.02</td>
<td>4.2</td>
<td>4.4</td>
<td>3.4</td>
<td>0.10</td>
</tr>
</tbody>
</table>

HR, heart rate (beats/min); SV, stroke volume (ml); PaoS, PaoD, PaoM, systolic, diastolic, and mean aortic pressures (mm Hg); R, resistance (dyne·sec/cm²); Zc, characteristic impedance (dyne·sec/cm²); Wt, total external power (mW); Wt/D, ratio of oscillatory to total power; LVEDP, left ventricular end-diastolic pressure (mm Hg); Pd/Pd, ratio of backward to forward wave amplitude; \(f_0\), frequency of first zero-crossing of impedance phase angle (Hz); Pr, propranolol; Ph, phentolamine.

\(\ast p<0.03, \dagger p<0.001\) vs. baseline values within each group.

\(\ast p<0.08, \dagger p<0.03; \ddagger p<0.001\) vs. normotensive baseline values.

\(\ddagger p<0.09, \ddagger p<0.05\) for baseline to propranolol changes between groups.

Values are mean±SD.

excess wave reflection could represent enough of a hemodynamic burden to result in deleterious effects on the heart.\(^6\)

Although we cannot rule out the possibility that higher doses of phentolamine might have further lowered blood pressure in the hypertensives to match normotensive values and thus might have completely decreased the wave reflection to normal, we believe that this is rather unlikely for several reasons. First, in our previous study, peripheral resistance was completely normalized with nitroprusside, whereas blood pressures in the hypertensives were lowered to roughly the same levels as in the present study (approximately 10 mm Hg higher than in the normotensive controls; see Table III in Reference 3). Nevertheless, the amount of wave reflection was completely normalized. Second, in that study, we verified that changes in wave reflections were not directly related to the levels of blood pressure. Specifically, in both normotensive and hypertensive groups, increasing blood pressure by approximately 20 mm Hg had no effect on the wave reflection index. Thus, it appears that the wave reflections are affected more by the level of smooth muscle tone (which is manifested in peripheral resistance) than by the level of blood pressure per se.

It is difficult, however, to infer that the increased wave reflections are caused by or arise from the sites of increased peripheral resistance. First, recent studies indicate that the major site of wave reflection in both normotensive and hypertensive humans appears to be near the renal arteries rather than more distal.\(^{31,32}\) Second, these are examples in which resistance and wave reflection responses are directionally different.\(^{29}\) Third, there is recent evidence that the major sites of peripheral resistance may be at vessels that are larger than arterioles.\(^{33}\) Thus, it is unclear how and where increased smooth muscle tone results in increased wave reflections. Because increased wave reflections can be produced by regional mismatches in vessel wall properties or diameters, it may be that essential hypertension results in regional variations in smooth muscle tone. Alternatively, it is possible that the magnitude of the peripheral wave reflections are not different in normotensives and hypertensives but that excess smooth muscle tone in hypertensives alters the normal attenuation properties of the large vessels to allow the wave reflection to be manifested at the aortic root more in hypertensives than in normotensives. Regardless, we cannot determine from our data the specific mechanism or site for this increased wave reflection.

The present findings together with the demonstration that wave reflection and resistance were completely normalized during nitroprusside administration\(^3\) suggest that there is some residual smooth muscle tone after combined blockade. Thus, either the \(\alpha\)-blockade is not complete or there is a nonadrenergically mediated component of vasoconstriction in the hypertensives. We cannot directly address the issue of completeness of the \(\alpha\)-blockade because we did not wish to challenge these hypertensive subjects with an \(\alpha\)-agonist. Furthermore, because some of the patients who received the higher doses began to experience some side effects of the drugs (nausea, abdominal cramps, dizziness, and so on), we did not think that it was prudent to use higher doses. Nevertheless, some insight into the extent of blockade can be gained by comparing our results with those in the literature. Studies using single 20- or 50-mg intravenous doses of phentolamine inhibited 50–75% of the pressor response to norepinephrine infusion.\(^{34,35}\) These studies are difficult to directly compare with ours because \(\beta\)-blockade was not induced first. A
study more directly comparable to ours examined hypertensive subjects after atropine and propanolol (0.2 mg/kg) administration and found a resistance decrease of 12% and a mean blood pressure decrease of approximately 10 mm Hg after a single intravenous bolus of 15 mg phentolamine. Challenge of the blockade with norepinephrine revealed approximately 65% effective blockade of the pressor response. Because our dose was substantially higher than this in all except two subjects and the average decreases in resistance and mean pressure were approximately 25% and 24 mm Hg, respectively, we suspect that we achieved a substantially greater extent of α-blockade than documented in that study. Additional indirect evidence for the adequacy of our blockade comes from the following consideration. If we estimate the blood concentration using a cardiac output of approximately 5 l/min and only the last infusion rate of 3–9 mg/min (which underestimates the true concentration because the effects of phentolamine at these dosages last from many minutes to 1 hour or more), the estimated blood concentration would be approximately 600–1,800 ng/ml. This is well above the concentration of 50 ng/ml that is needed to block central (neurally) mediated vasoconstriction. This concentration is, in turn, about 12-fold that needed to block the effects of circulating catecholamines. Thus, although we do not have the definitive answer as to the completeness of blockade, our study suggests the intriguing possibility that there may be factors not mediated by the adrenergic system, such as hormonal or neural mediators, that are responsible for the increased smooth muscle tone and hence altered hemodynamics in essential hypertension.

We recognize that it may not be warranted to extrapolate our findings from this specific population,
which had been studied in the supine position after intravenous infusion of an agent with nonspecific \( \alpha \)-adrenergic antagonistic actions, to other settings. Nevertheless, if borne out by future studies, the basic principles demonstrated here could have important implications for treating hypertension with chronically administered, more selective \( \alpha \)-adrenergic agents whether they are central agonists such as clonidine or postsynaptic \( \alpha_1 \)- or \( \alpha_2 \)-antagonists. This is because all of these agents share blocking of peripheral vasoconstriction as a final common pathway. As our data imply, merely lowering blood pressure into the normal range with drug doses that can be tolerated may not completely normalize some of the other hemodynamic alterations, such as wave reflections. It behooves physicians and researchers to consider the known advantages and disadvantages of any class of antihypertensive agents. Otherwise, merely treating blood pressure as an end point may result in long-term deleterious effects despite seemingly “well controlled” hypertension.

**References**


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Arterial hemodynamics in human hypertension. Effects of adrenergic blockade.
C T Ting, C Y Chou, M S Chang, S P Wang, B N Chiang and F C Yin

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