Hypertension Clinical Studies

Hemodynamics of the Carotid Artery After Vasodilation in Essential Hypertension

STÉPHANE LAURENT, PATRICK LACOLLEY, GÉRARD LONDON, AND MICHEL SAFAR

SUMMARY We performed simultaneous noninvasive measurements of common carotid artery and brachial artery hemodynamics in nine normal subjects and 10 subjects with sustained essential hypertension. In hypertensive subjects, brachial artery blood flow and forearm vascular resistance were in the normal range while carotid artery blood flow and carotid artery resistance were decreased and increased, respectively. The most important findings were the changes in the internal caliber of large arteries. Although the brachial and carotid artery diameters of hypertensive subjects were measured for the same level of mean arterial pressure, brachial artery diameter was significantly increased and carotid artery diameter was strictly normal as compared with values found in normal subjects. To assess whether carotid artery circulation could influence the baroreceptor reflex response to arteriolar vasodilation, carotid artery and brachial artery hemodynamics were measured in immediate succession in normotensive and hypertensive subjects before and after oral administration of cadralazine, a dihydralazine derivative. After cadralazine treatment, carotid artery tangential tension decreased in hypertensive subjects, and the changes were significantly correlated to the increase in heart rate. A similar correlation was found in normal subjects, but it was reset toward higher heart rates. These results indicate that the carotid artery does not behave like the brachial artery in response to a chronic increase in blood pressure. This behavior indicates intrinsic alterations of the arterial wall and might be involved in the resetting of the carotid baroreceptor reflex. Carotid artery circulation could play a role in hypertension by modulating the carotid baroreceptor mechanisms involved in the response to drug-induced arteriolar vasodilation. Whether these findings represent a primary or a secondary event remains to be determined. (Hypertension 11: 134-140, 1988)

KEY WORDS • large arteries • essential hypertension • baroreceptor reflex mechanisms • pulsed Doppler • carotid circulation

THE response of the common carotid artery (CCA) and the brachial artery (BA) to a chronic elevation of blood pressure may differ according to the regional circulation. Using a noninvasive pulsed Doppler system, we evaluated arterial diameter and blood flow of the straight superficial arteries. We measured simultaneously CCA and BA hemodynamics in normal and hypertensive subjects to assess the effect of essential hypertension on circulation in these arteries.

The decrease in blood pressure and vascular resistance observed after treatment with dihydralazine or its derivative, cadralazine, was related to the dilation of small arteries, as has been shown extensively for dihydralazine and other derivatives.1,2 Interestingly, in previous studies3 we observed that BA diameter was reduced after dihydralazine or cadralazine treatment, in contrast to the changes observed in response to other vasodilators, such as nitroglycerin or calcium inhibitors, which increased BA diameter.4 Pharmacological research1,2 and previous studies from our laboratory3,4 have suggested that activation of the sympathetic nervous system leads to active vasoconstriction of the BA, in addition to inducing passive vasoconstriction following reduction in blood pressure. Indeed, activation of reactive vasoconstriction may greatly limit the therapeutic hypotensive response to vasodilator administration in hypertensive patients.4,5

Our main purpose in the present study was to assess whether CCA circulation could influence the baroreceptor reflex response to arteriolar vasodilation. Hemodynamics of the CCA and the BA were measured in immediate succession in 10 subjects with essential hypertension before and after oral administration of ca-
dralazine. To further analyze the baroreceptor reflex response to arteriolar vasodilation, these results were compared with those obtained in nine normotensive subjects.

**Subjects and Methods**

Nineteen subjects were included in the study: 9 normotensive subjects (7 men and 2 women) and 10 subjects (8 men and 2 women) with sustained essential hypertension. The mean ages of the two populations were similar (38 ± 1 and 42 ± 3 [1 SEM] years, for normal and hypertensive subjects, respectively), and the two groups did not show any significant difference in height (1.73 ± 0.02 vs. 1.69 ± 0.02 m), weight (63 ± 4 vs. 72 ± 4 kg), and body surface area (1.85 ± 0.06 vs. 1.86 ± 0.05 m²). All hypertensive subjects were untreated or had discontinued their therapy at least 20 days before the study. Diastolic blood pressure remained constantly above 95 mm Hg during the untreated ambulatory period. Subjects had no sign, symptom, or history of heart or renal failure, coronary insufficiency, neurological disorders, or major diseases other than hypertension. Subjects were considered to have essential hypertension on the basis of previously described extensive investigations. Stenosis of extracranial cerebral arteries was excluded in all subjects on the basis of continuous Doppler examination. Informed consent was obtained from each subject after a detailed description of the procedure.

The study began at 0900 during 1-day hospitalization. The hemodynamic study was performed at controlled room temperature of 20 ± 0.5°C, after 30 minutes of rest, with the subject in the recumbent position. Hemodynamic measurements were done before and 4 hours after administration of an oral dose (20 mg) of cadralazine, according to the pharmacokinetic and pharmacodynamic effects of the drug. Arterial blood pressure was measured automatically every 2 minutes in the left arm with an oscillometric blood pressure recorder (Dinamap, Model 845, Critikon, Tampa, FL, USA). The same values were found for blood pressure in the left arm and in the right arm. Heart rate (HR) was determined using a continuous electrocardiographic monitor (Electronics for Medicine, Honeywell, Pleasantville, NY, USA). Mean arterial pressure (MAP) was determined as the pressure corresponding to the maximum amplitude of oscillations. The standard deviation of MAP was 4 ± 1% for 10 measurements during a 20-minute period (expressed as a percentage of the mean). In normal and hypertensive subjects, hemodynamic measurements were performed first on the right CCA then on the right BA within 15 minutes, during which blood pressure remained stable. No significant changes in systolic pressure, diastolic pressure, MAP, or HR occurred when the two periods were compared.

Carotid and forearm hemodynamic values were obtained with a bidimensional pulsed Doppler system (Alvar Electronics, Montreuil, France) whose probe was fixed with a stereotactic device over the course of the right CCA or the BA, as previously described and validated. This apparatus enabled the diameter and the blood velocity of the artery to be measured according to two fundamental characteristics: a bidimensional recording of the Doppler signals and a range-gated time system of reception. The former was obtained with a probe containing two transducers, which formed between them a 120-degree angle, so that when Doppler signals recorded by each transducer were equal in absolute value, the ultrasonic incidence with the vessel axis was 60 degrees. With the second characteristic, it was possible to select the length of delay from the emission and the duration of the reception and to convert this time echographically into the depth and the width of the Doppler measurement volume. A pedal incorporated into the apparatus enabled the investigator to vary automatically the depth and the width of the measurement volume by incremental or decremental steps of 0.4 mm.

To determine the arterial diameter, the width of the measurement volume was reduced to the smallest convenient value (about 0.4 mm) with sufficient reflected energy, and its depth from the transducer was progressively increased step by step. This procedure was continued across the lumen of the artery with a small measurement volume and permitted the recording of velocities of the different stream lines involved in the arterial flow. Thus, the first and last Doppler signals recorded when crossing the vessel corresponded to the vessel walls, and the difference in depth between these two signals represented the internal arterial diameter. To take into account the ultrasonic incidence angle, a correction was made by multiplying this difference by sinus 60 degrees, 60 degrees being the adequate angle used in the measurement. Arterial diameter was expressed in centimeters, with a reproducibility of 3 ± 1%. Once the arterial diameter was determined, the velocity of the whole arterial blood column was measured. For this measurement, the width of the measurement volume was increased to the value of the arterial diameter; its depth from the transducer was adjusted to superimpose the measurement volume and the lumen of the artery. The arterial blood velocity was expressed in centimeters per second, and mean arterial blood velocity was integrated electronically. CCA blood flow and BA blood flow were calculated as the product of the blood velocity and cross-sectional area deduced from the arterial diameter (D) by using a cylindrical representation of the artery (S = 3.14 D²/4). Arterial blood flow was expressed in milliliters per minute. Local vascular resistance (mm Hg·sec·ml⁻¹) was calculated as the ratio between simultaneous mean blood pressure and mean blood flow. Tangential tension (T) of the CCA or the BA was defined, according to the law of Laplace, as T = MAP × D²/2 and was expressed in mm Hg·cm⁻¹. The change in tangential tension was the difference in tension before and after cadralazine treatment (expressed as a percentage of basal value in Figure 3).

Blood samples for plasma renin activity (PRA) measurement were taken from an indwelling catheter be-
before and 4 hours after administration of 20 mg of cadralazine. PRA was assessed by radioimmunoassay as previously described.17

For the statistical evaluation, the Wilcoxon test for unpaired data was used to compare hypertensive subjects and normal subjects.18 Results were expressed as means ± 1 SEM. The Wilcoxon test for paired data was used to compare basal and drug-treatment values. When relationships between hemodynamic parameters existed for both normotensive controls and hypertensive subjects, regression lines were compared using analysis of covariance (ANCOVA).18

Results

Baseline Hemodynamics

In hypertensive patients, diameter of the BA was increased compared with that in normotensive subjects (0.489 ± 0.013 vs 0.445 ± 0.013 cm; p < 0.05; Table 1). Mean blood flow velocity and volumic blood flow of the BA did not change significantly. Vascular resistance was not significantly increased, but tangential tension of the BA was increased in hypertensive subjects (p < 0.01). Diameter and mean blood flow velocity of the CCA were comparable between the two groups; however, volumic blood flow of the CCA was slightly decreased (p < 0.05) and vascular resistance and tangential tension were increased in hypertensive subjects (p < 0.01). PRA was not significantly different in normal subjects as compared with hypertensive subjects.

Hemodynamic Effects of Cadralazine in Normotensive Subjects

Blood Pressure, Heart Rate, and PRA

Systolic pressure, diastolic pressure, and MAP did not change in normotensive subjects, HR and PRA increased significantly (p < 0.01; Figure 1). The change in PRA was significantly and positively correlated with the change in HR (r = 0.861, p < 0.01).

Brachial Artery Circulation

In normotensive subjects, no change in diameter, mean blood flow velocity, volumic blood flow, local vascular resistance, or tangential tension of the BA was statistically significant. There was a significant relationship (r = −0.667, p < 0.05) between initial forearm vascular resistance and changes after cadralazine treatment: the greater the initial resistance, the greater the decrease (Figure 2). In three subjects, forearm vascular resistances, initially the lowest of the group, increased slightly after cadralazine treatment.

Common Carotid Artery Circulation

In normotensive subjects, no significant change in diameter, mean blood flow velocity, volumic blood flow, or local vascular resistance occurred in the CCA. Mean tangential tension in the CCA did not change; however, when individual changes in tangential tension were considered, there was a significant relationship (r = −0.809, p < 0.01) between change in CCA tangential tension and change in HR: the greater the decrease in tangential tension, the greater the increase in HR (Figure 3).

Discussion

To our knowledge, the present study was the first to evaluate simultaneously, under basal conditions, brachial and carotid arterial hemodynamics in age-matched and sex-matched normal and hypertensive subjects. CCA blood flow and vascular resistance were decreased and increased, respectively, in hypertensive subjects as compared with normotensive subjects, while BA blood flow remained within the normal range and forearm vascular resistance was not significantly increased in hypertensive subjects. This lack of a significant change could have been due to the smallness of the samples. However, as reported by others19-21 and by our co-workers,13,14,22 BA volumic blood flow in essential hypertensive subjects was not significantly different from values in normotensive subjects.
TABLE 1. Hemodynamic Parameters Before and After Cadralazine Treatment in Normotensive and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Hemodynamic parameter</th>
<th>Normotensive subjects</th>
<th>Hypertensive subjects</th>
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<tbody>
<tr>
<td></td>
<td>Before C</td>
<td>After C</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>114±3</td>
<td>116±3</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>71±3</td>
<td>68±3</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>85±3</td>
<td>84±3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>64±4</td>
<td>79±4*</td>
</tr>
<tr>
<td>PRA (ng Ang I/ml/hr)</td>
<td>1.3±0.4</td>
<td>4.5±0.9*</td>
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BA circulation

| D (cm)                | 0.445±0.013 | 0.470±0.019 | 0.489±0.013∥ | 0.471±0.022∥ |
| V (cm/sec)            | 5.7±1.4     | 4.4±0.8     | 6.0±1.1     | 6.9±1.2     |
| F (ml/min)            | 53±14       | 46±8        | 71±18       | 75±15       |
| R (mm Hg-sec·ml⁻¹)    | 163±41      | 103±15      | 199±38      | 143±26†     |
| T (mm Hg·cm)          | 18.9±0.9    | 19.1±1.1    | 30.3±1.3*   | 26.6±1.9†   |

CCA circulation

| D (cm)                | 0.663±0.19  | 0.666±0.19  | 0.629±0.19  | 0.624±0.15  |
| V (cm/sec)            | 21.8±1.9    | 23.9±2.2    | 18.2±1.1    | 18.9±1.1    |
| F (ml/min)            | 448±35      | 490±37      | 340±26∥     | 346±23      |
| R (mm Hg-sec·ml⁻¹)    | 11.8±1.0    | 10.1±0.9    | 23.2±1.4*   | 20.6±1.4‡   |
| T (mm Hg·cm)          | 27.9±1.3    | 27.1±1.2    | 39.2±1.6*   | 35.8±1.6†   |

Values are means ± SEM. SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate; Ang I = angiotensin I; BA = brachial artery; CCA = common carotid artery; D = diameter; V = mean blood flow velocity; F = volumic blood flow; R = local vascular resistance; T = tangential tension.

* p<0.01, ‖ p<0.05, compared with pretreatment values in normotensive subjects (by paired and unpaired t tests).

† p<0.01, ‡ p<0.05, § p<0.001, compared with pretreatment values in hypertensive subjects (by paired t test).

FIGURE 1. Set point for normotensive subjects (pretreatment, ○; posttreatment, ●) and hypertensive subjects (pretreatment, ○; posttreatment, ●) before and 4 hours after oral administration of cadralazine (20 mg). The set point is defined as the value of heart rate occurring at a definite level of MAP under steady state conditions.

The most important findings observed under basal conditions were the changes in the internal caliber of the large arteries. Although the diameters of the BA and CCA of hypertensive subjects were measured at the same level of MAP, BA diameter was significantly increased and CCA diameter was strictly normal.

Since an increase in arterial diameter is expected from the simple mechanical effect of the elevated blood pressure, the latter finding clearly indicates an intrinsic change in the viscoelastic properties of the hypertensive CCA wall. Increased rigidity or thickness, or both, of the arterial wall might explain the lack of...
increase in CCA diameter. The latter possibility results from the simple application of the Laplace law in the hypertensive carotid circulation and is consistent with the observation that, in hypertensive human carotid arteries, a tetraploid state of smooth muscle cells has been recognized, indicating an increase in the mass of arterial smooth muscle. Wall thickness, connective tissue content, and mechanical stiffness are increased in the arteries of hypertensive humans and animals. The CCA may have different mechanical properties than the BA, as suggested by histological findings. Indeed, in the dog, the collagen/elastin ratio was increased in the carotid as compared with the femoral artery (which can be compared with the BA since it supplies blood flow to a limb). Thus, the different proportions of elastin and collagen in the carotid wall may explain the different response to chronic elevation of blood pressure, as compared with that in the BA. Pharmacological data favor functional or structural differences between CCA and BA and suggest differences in the vascular responsiveness of the CCA and the BA to circulating hormones. As shown in previous studies, and in the present one, cadrzalazine treatment decreased BA diameter and did not change CCA diameter, nitrendipine increased BA diameter and did not change CCA diameter, and isosorbide dinitrate and Captopril increased both BA and CCA diameters. Thus, for the same decrease in MAP, the response of CCA may differ from one vasodilator to another.

From these findings, several consequences may be proposed as far as the carotid baroreceptor reflex mechanisms are concerned. First, the lack of increase in CCA diameter might contribute to decreasing the resting baroreceptor activity in spite of the higher resting blood pressure. Indeed, CCA tangential tension, already enhanced by the rise in MAP, would have been greater if CCA diameter had been increased. Second, increased thickness and rigidity of the hypertensive arterial wall may affect not only the afferent component of the baroreceptor reflex (a given pulse pressure should produce less wall motion, less change in wall stress, and less deformation of receptor endings than could occur in normotensive subjects) but also the effector component.

In the present investigation, the dihydralazine-like substance cadrzalazine was used to assess whether changes in CCA circulation could influence the baroreceptor reflex response secondary to arteriolar vasodilation. Before any discussion of the problem, it is important to note that the hemodynamic and neurogenic adaptive mechanisms following cadrzalazine administration are probably very complex. Cadrzalazine, like dihydralazine, is known to induce both an arteriolar dilatation and sympathetic nervous system activation. In hypertensive subjects, the observed decrease in brachial and carotid vascular resistance is consistent with the former effect. The latter is suggested by the increase in HR and PRA and the strong correlation between these two parameters. The study was performed not in acute but in steady state conditions, namely, before and 4 hours after oral administration of cadrzalazine. Thus, the observed arteriolar dilatation must be considered the net result of direct effects of the drug and indirect counteracting effects related to reflex sympathetic activation. Furthermore, in the present study, the baroreceptor reflex response involved not only carotid baroreceptors but also aortic receptors and mechanoreceptors of the low pressure system, the participation of which is difficult to appreciate.

We cannot exclude the role of the aortic baroreceptors, which may have been affected differently from the carotid baroreceptors during the process of hypertension or after cadrzalazine treatment. However, that we found a significant relationship between the change in CCA tension and HR in hypertensive subjects suggests that changes in aortic arch tension may have influenced HR in a parallel manner. Indeed, if reflex tachycardia was mediated differently by changes in aortic and CCA tension and therefore was the net result of these different influences, we would not have found, in response to a common stimulus, a relationship between HR and changes in tension at the level of one baroreceptor area only. Thus, the observed results must be considered the consequence of an integrated response, where the role of the changes in CCA tangential tension is difficult to assess.

It was the first time, to our knowledge, that CCA tangential tension instead of MAP was used as an index of baroreceptor changes in a clinical study. The reliability of changes in carotid tangential tension as an index of baroreceptor changes should be accepted in the present study. First, whether the carotid sinus...
nerve endings respond to tensile deformation or to tensile stress has not entirely been resolved, since data favoring a response to deformation rather than to stress were obtained in arteries with large diameters and not at physiological pressures of more moderate dimensions. The present study favors the role of tensile stress; however, measurements were made at the level of the CCA, which, although bearing some afferences, has a different structure from the carotid sinus. Second, the good reproducibility of the measurement of carotid tangential tension allowed us to consider the relationship between changes in CCA tangential tension and change in HR. Indeed, CCA tangential tension was calculated as the product of CCA radius and MAP. Reproducibilities of measurements of CCA diameter and MAP were 3 ± 1 and 4 ± 1%, respectively. Changes in CCA tangential tension were expressed as a percentage of the initial value to take into account morphological differences in CCA diameter in the whole population.

Another important finding of the present study was the strong relationship between the change in HR and in CCA tangential tension after cadralazine administration. The finding concerned exclusively CCA tangential tension, since no comparable relationship was observed between 1) the change in HR and 2) the change in MAP or in CCA diameter. Since no direct stimulating effect of hydralazine and derivatives on the isolated heart has been reported, the result clearly suggests that cadralazine-induced sympathetic activation is related to modifications of carotid artery hemodynamics. A common factor, the reduction in MAP, could account for both the decrease in CCA tangential tension and the increase in HR. However, the change in MAP was not correlated with the change in HR. Another common factor could be involved, such as the activation of the autonomic nervous system by cadralazine, leading to an increase in HR and to vasoconstriction of large arteries. Indeed, in three normotensive subjects, HR increased without a concomitant significant change in CCA tangential tension. In addition, a cause-effect relationship between changes in CCA tangential tension and changes in HR might be possible, according to the classic baroreceptor reflex mechanisms. In favor of this interpretation is the fact that the vasodilators captopril and isosorbide dinitrate, which increase CCA diameter, do not change HR. Thus, it seems likely that the cadralazine-induced sympathetic activation may be initiated or potentiated by modifications in the carotid artery hemodynamics.

The relationship between the change in CCA tangential tension and the change in HR that was observed in normotensive subjects was significantly different from that observed in hypertensive subjects (see Figure 3). In normotensive subjects, changes in HR were significantly correlated with changes in CCA tangential tension (see Figure 3). Interestingly, a marked increase in HR occurred without a concomitant change in CCA tangential tension in two subjects; in three other subjects, both HR and CCA tangential tension increased. It is likely that, in the absence of a fall in MAP in normotensive subjects (see Table 1), an additional effect of cadralazine on HR, independent of change in CCA circulation, was unmasked. No direct stimulating effect of hydralazine and its derivatives on the isolated heart and no atropinelike effect of cadralazine have been reported. A differential effect of cadralazine on sinocarotid and aortic baroreceptors is unlikely, since MAP did not change. Therefore, a central mechanism of action, in addition to the peripheral vasodilating effect, is a possible explanation, as already suggested by earlier experimental works. Indeed, the increase in HR after cadralazine treatment could be due to sympathetic stimulation or to parasympathetic withdrawal, or to both, based on a neurogenic imbalance of central origin. Finally, the significant relationship between the change in HR and change in CCA tangential tension suggests, in both normal and hypertensive subjects, that the level of tangential tension, although not the only cause of the reflex tachycardia, may still influence the HR response. The interpretation of the data is even more difficult because only one stimulus, rather than a stimulus response curve of baroreceptor reflex activation was performed in this study. It cannot be excluded that the two groups of subjects are at different levels of the stimulus response curve. This disparity could explain the difference in tachycardia in response to the change in MAP from one group to another.

In conclusion, the present study has shown that the CCA circulation seems to play a role in hypertension by modulating the carotid baroreceptor mechanisms involved in the response to drug-induced arteriolar vasodilation. Whether these findings represent a primary mechanism or a secondary event remains an open question and requires further investigation.

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