Systemic and Arterial Hemodynamic Effects of Nifedipine (20 mg) in Mild-to-Moderate Hypertension

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SUMMARY Systemic and arterial hemodynamic effects of the new 20 mg tablet of nifedipine were studied in seven patients with mild-to-moderate essential hypertension. Hemodynamics of the forearm arterial circulation were investigated using a new pulsed Doppler system, enabling the simultaneous determination of the brachial artery diameter and the arterial blood flow velocity. After nifedipine administration, blood pressure decreased significantly, due to a fall in total peripheral resistance. Simultaneously, brachial blood flow increased significantly, due both to an increase in arterial diameter and blood flow velocity. The study provided evidence that, with nifedipine, there is both 1) a dilation of small arteries, causing a decrease in blood pressure; and 2) a dilation of peripheral large arteries, leading to an increase in peripheral blood flow.

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KEY WORDS • essential hypertension • peripheral blood flow • calcium antagonists • pulsed Doppler

The antihypertensive effect of the calcium-channel blocker, nifedipine, is well established.¹ Most studies indicate that the 10 mg tablet given orally causes a rapid decrease in blood pressure. However, the duration of action is relatively short.² Recent studies³ have shown that the drop in pressure during recumbency is significantly larger and lasts longer for 60 mg than for 40 and 20 mg of the drug. For this reason, it seemed reasonable to investigate the hemodynamic effects of the 20 mg new nifedipine tablet given orally. Since calcium antagonists interfere with the excitation-contraction coupling of smooth muscle by blocking the entrance of calcium into the cell,⁴ a particular attempt has been made to evaluate the arterial effects of the drug. For this, a new pulsed-Doppler system has been used, enabling a simultaneous determination of the diameter and the blood flow velocity in the brachial artery.⁵,⁶

Material and Methods

Patients

Seven hypertensive men were included in the study. Median age was 44 ± 3 years (+ 1 standard error of the mean). Mean body surface area was 1.90 ± 0.05 m².

The patients were hospitalized for a 7-day period on a 100 mEq/day sodium diet. Antihypertensive treatment was discontinued at least 4 weeks before the study. During the untreated period, in all patients, ambulatory lying diastolic blood pressure was equal to or higher than 100 mm Hg in at least three consecutive measurements. Before the study, a complete clinical and laboratory evaluation had been carried out, including physical examination, routine laboratory tests, determination of urinary catecholamines, measurement of plasma and urinary electrolytes, and intravenous timed-pyelography. All patients were diagnosed as having moderate essential hypertension; creatinine clearance was normal (greater than 90 ml/min), the optic fundi showed no hemorrhages, exudates and/or papilledema. None of the patients had clinical signs of congestive heart failure, coronary insufficiency, valvular heart disease, or stroke. The protocol was approved by INSERM (Institut National de la Santé et de la Recherche Médicale). Informed consent for the investigations was obtained from the patients after a detailed description of the procedure.

Hemodynamic Parameters and Systemic Arterial Compliance

The hemodynamic study was performed in the seven patients without premedication, after overnight fasting, on the third day of hospitalization. The room temperature was 22° ± 1°C. With the subject in the supine position, a transcutaneous catheter was inserted into the left antecubital veins, for the injection of indocyanine green. The investigation began at least 30 minutes after insertion of the catheter.
Arterial pressure was recorded on a Thomson Telco apparatus via a metallic No. 18 hypodermic needle inserted into a brachial artery. The needle was connected to a Statham P23 db balanced resistive strain gauge via a special low compliance short 10 cm catheter of Teflon regularly flushed with heparinized Ringers solution. No significant distortion existed in the recorded signal. The system was checked with both time and frequency-domain measurements and showed a flat response beyond 80 Hz. Inspection on the oscilloscope of recorded curves over about 1 minute of time permitted representative and reproducible pressure pulses to be selected for analysis.

Cardiac output was determined in triplicate by the indocyanine green dye-dilution technique, using a Waters cuvette and densitometer, as previously described. It was expressed in ml/min/m² after correction for body surface area. The normal value of the laboratory for men between 25 and 45 years was 3535 ± 196 ml/min/m².

The procedure for the determination of systemic arterial compliance has been previously described and validated. Briefly, the arterial system can be treated as a simple first order model, which associates in series a capacitive element (C) and a resistive element (R). Such a model discharges monoeXponentially as a function of time, and the time constant (T) of the system, i.e., the reciprocal of the exponential slope discharge, represents the product of the capacitance (C) by the resistance (R):

\[ T = C \times R \]  
so that the compliance is calculated according to the formula

\[ C = \frac{T}{R} \]  

In practice, simultaneous measurements of R and T were necessary, according to equation 1. The resistance R was calculated as the total peripheral resistance (TPR) as follows:

\[ TPR \ (mm \ Hg/ml/s) = \frac{MAP}{CO}, \]  
where MAP is mean arterial pressure (mm Hg) and CO is the cardiac output (ml/s). The T value was calculated from the pulse pressure curve recorder at speeds of 100 mm/sec by correcting in semilogarithmic scale the pressure time curve during the last two-thirds of diastole. The correlation coefficient and the slope of the regression line were calculated. The reciprocal value of slope, or time-constant (T) of the system, was expressed in seconds and used as an evaluation of the steepness of the diastolic decay.

Blood pressure was recorded just before and immediately after the three cardiac output determinations, enabling three values of compliance to be calculated. Arterial compliance was the mean of the three values. The reproducibility of the methods was 10% ± 3%. The normal value of the laboratory for patients between 25 and 45 years was 1.26 ± 0.10 ml/mm Hg per m².

Arterial Hemodynamics

Arterial hemodynamics of the brachial artery were performed using a bidimensional pulsed Doppler system, as previously described and validated. The zero-crossing velocimeter, which is used in the study, operates at a frequency of 8 MHz and has two original features: 1) the pulsed emission is associated with an adjustable range-gated time system; and 2) a double transducer probe provides a bidimensional blood velocity measurement, which considerably minimizes the errors introduced by the observation angle between the ultrasonic beam and the velocity of the blood column.

Briefly, each of the two transducers acts alternatively as emitter and receiver. Between the emitted pulses, the transducer operates as a receiver and an electronic gate selects the signals reflected at a given time from the emission. This time represents the time delay of the reception. The reception duration can also be selected. Adjustments of time delay and reception duration are made using constant steps of half a microsecond. With such a system, it is possible to determine exactly the distance, d, between the red cells of the blood column and the transducer, according to the echographic relation

\[ d = \frac{c}{2} \times t, \]

where \( c \) is the ultrasound speed in tissues and \( t \) the reception time. The time delay and the duration reception represent, respectively, the depth and the thickness of the measurement volume along the ultrasound beam axis. With this procedure, it is possible to determine the diameter of the vessel and the cross-sectional blood flow velocity.

The double transducer system overcomes the difficulty of measuring the angle between the ultrasonic beam and the vessel axis. The probe contains two transducers set at a known angle one to the other; in the present system, this was 120°. Probe position is adjusted until two successive velocities, one from each transducer, are equal in absolute value. The angle \( \theta \) between each ultrasonic beam and the vessel axis is then equal to \( \alpha/2 \). In such conditions, the error from the determination of angle \( \theta \) is less than 2%. Once the correct position has been found, the probe can be fixed by means of a stereotaxic device placed around the arm. In a previous study, the accuracy of the Doppler determinations has been studied with a hydraulic test device using calibrated latex tubes. So, it has been shown that: 1) the velocity measured with the studied system was within 95% of the known velocity for flow velocities between 5 and 100 cm/sec, and 2) the overestimation of the arterial diameter due to the sample volume size was 0.035 ± 0.015 cm, a number that was not significantly different from zero.

In clinical practice, subjects were examined in the supine position at a constant room temperature of 22° ± 1°C after a preliminary rest period of 20 minutes and just before the output determinations. The arm was placed in a horizontal plane corresponding to a third of the distance up from the examination table to the anterior chest wall. An ultrasonic gel was used as coupling medium between the probe and the skin. The Doppler signals were monitored throughout the examination by...
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A loud speaker and recorded on paper with a Siemens apparatus. With the probe properly placed, the arterial walls were located by changing the time delay step by step with the step advance synchronized with the electrocardiogram. Thus, the interval between the successive waves corresponded to the step advance of the time delay. If $\Delta t$ is the difference between the distal and proximal walls, the diameter $D$ is equal to $D = c/2 \times \Delta t \sin \theta$, where $c$ is the ultrasonic speed (1540 m/sec) and $\theta$ the angle between the ultrasonic beam and the vessel axis.

Cross-sectional blood velocity was measured with the time delay adjusted to the depth of the proximal and distal walls, the diameter $D$ is equal to $D = c/2 \times \Delta t \sin \theta$, where $c$ is the ultrasonic speed (1540 m/sec) and $\theta$ the angle between the ultrasonic beam and the vessel axis.

Systemic hemodynamics are indicated in table 1. Before the drug administration, intraarterial MAP measured on the 3rd day of hospitalization was equal or above 100 mm Hg in all cases, and diastolic pressure was greater than 80 mm Hg in six patients. After nifedipine, blood pressure decreased significantly. The decrease in systolic pressure was more significant ($p < 0.01$) than the decrease in diastolic pressure ($p < 0.05$). Total peripheral resistance significantly decreased ($p < 0.01$). Cardiac index and heart rate slightly increased ($p < 0.05$), while stroke index did not change. Systemic arterial compliance increased from 0.78 $\pm$ 0.11 to 0.92 $\pm$ 0.10 ml/mm Hg.m$^2$ ($p < 0.02$).

After nifedipine, the diameter of the brachial artery significantly increased, from 0.480 $\pm$ 0.03 to 0.535 $\pm$ 0.03 cm ($p < 0.01$). Blood flow significantly increased ($p < 0.02$), due both to an increase in arterial diameter and in blood flow velocity ($p < 0.05$). Forearm resistance decreased significantly, from 63 $\pm$ 9 to 31 $\pm$ 5 mm Hg/ml/sec ($p < 0.01$).

Table 1. Effects of Nifedipine (20 mg) on Systemic and Arterial Hemodynamics

<table>
<thead>
<tr>
<th>Patients</th>
<th>SAP (mm Hg)</th>
<th>DAP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>HR (bpm)</th>
<th>CI (ml/min/m$^2$)</th>
<th>SI (ml/m$^2$)</th>
<th>TPR (dyn/sec/cm$^{-5}$m$^2$)</th>
<th>SAC (ml/mm Hg.m$^2$)</th>
<th>Diameter (cm)</th>
<th>Velocity (cm/sec)</th>
<th>Blood flow (ml/min)</th>
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<td>183</td>
<td>100</td>
<td>128</td>
<td>67</td>
<td>2807</td>
<td>42</td>
<td>3648</td>
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<td>0.480</td>
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<td>89</td>
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<tr>
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<td>166</td>
<td>99</td>
<td>121</td>
<td>75</td>
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<tr>
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<td>107</td>
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<tr>
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<tr>
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<td>111</td>
<td>84</td>
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<tr>
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<tr>
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<tr>
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<tr>
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<td>56</td>
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<td>3140</td>
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<tr>
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<td>57</td>
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<td>47</td>
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<tr>
<td>B</td>
<td>171</td>
<td>91</td>
<td>118</td>
<td>74</td>
<td>3444</td>
<td>46</td>
<td>2864</td>
<td>0.78</td>
<td>0.480</td>
<td>12.5</td>
<td>128</td>
</tr>
<tr>
<td>±10 ±4 ±6 ±5 ±35 ±2 ±265 ±0.11 ±0.034 ±2.0 ±21</td>
<td>A</td>
<td>154</td>
<td>82</td>
<td>106</td>
<td>78</td>
<td>3749</td>
<td>48</td>
<td>2309</td>
<td>0.92</td>
<td>0.335</td>
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<tr>
<td>±9 ±9 ±6 ±5 ±96 ±3 ±157 ±0.10 ±0.032 ±2.7 ±36</td>
<td>p value</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.02</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.02</td>
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</tbody>
</table>

Abbreviations: SAP = Systolic arterial pressure; DAP = Diastolic arterial pressure; MAP = Mean arterial pressure; HR = Heart rate; CI = Cardiac index; SI = Stroke index; TPR = Total peripheral resistance; SAC = Systemic arterial compliance; B = Before drug; A = After drug.
Discussion

In the present investigation, nifedipine produced a significant decrease in blood pressure, due to a fall in total peripheral resistance and therefore in arteriolar dilation. However, in addition to its action on small arteries, nifedipine also had important effects on the peripheral large arteries.

It is well established that a decrease in blood pressure may have two important mechanical consequences on the arterial system. First, the fall in pressure is accompanied by a decrease in arterial diameter, due to the passive effect of the blood pressure reduction and/or to the active alpha-vasoconstriction related to the baroreflex response.

Second, according to the Hallock and Benson experiments, any decrease in blood pressure is followed by an increase in arterial compliance, i.e., the product between arterial distensibility and arterial volume. Since the arterial diameter, and consequently the arterial volume, is reduced, the increase in arterial compliance is due to an exclusive increase in arterial distensibility, as the mechanical consequence of the decrease in pressure.

The results obtained with nifedipine clearly contrasted with those expected from a simple mechanical decrease in blood pressure. First, the arterial diameter significantly increased during the systemic administration of nifedipine. Second, systemic arterial compliance significantly increased. The increase in arterial diameter was not due to a simple effect on arterial distensibility but involved also an increase in arterial volume, related to the pharmacological effect of the drug. Such a peculiar action of nifedipine on the compliance of large arteries possibly explains the 30 mm Hg decrease in systolic pressure, which contrasts with the borderline significance of the decrease in diastolic pressure.

After nifedipine administration, a baroreflex response involving an increase in heart rate and cardiac output was observed as a consequence of the fall in pressure. The increase in heart rate was smaller in magnitude than the tachycardia observed with the classical 10 mg nifedipine tablets. The lesser tachycardia observed in the supine position could result from the increase in arterial diameter, which could modify the distortion of the arterial wall, leading to a lesser decrease in the tension of the arteries that would be expected from the decrease in pressure. Since the baroreflex response is rather mediated by the distortion of the arterial wall than by the decrease in blood pressure as an exclusive cause, the observed increase in arterial diameter could minimize the activation of the baroreflex mechanisms and therefore the observed increase in heart rate.

One of the dominant finding of the study was the increase in brachial blood flow, due both to an increase in arterial diameter and an increase in blood flow velocity. Such an action of nifedipine contrasts with the results observed with the other vasodilating drugs. Di- hydralazine, which reduces the arterial diameter with no change in blood flow velocity, does not modify brachial blood flow. Nitroglycerin, which dilates the peripheral large arteries markedly, does not change blood velocity and flow volume in the brachial artery. Only the calcium antagonist agent, diltiazem, has a comparable effect on peripheral blood flow. However, the increase in blood flow is somewhat less than with nifedipine, since the increase in arterial diameter is associated with only a slight and insignificant increase in blood flow velocity. Finally, the significant increase in peripheral blood flow caused by nifedipine makes it possible to obtain with an antihypertensive drug both a decrease in blood pressure and an improvement in peripheral circulation.

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References

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