Effect of Bisoprolol on Blood Pressure and Arterial Hemodynamics in Systemic Hypertension

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Blood pressure, heart rate, common carotid and brachial arterial hemodynamics using pulsed Doppler flowmetry and pulse wave velocity determinations were evaluated using a double-blind crossover design versus placebo in 14 patients with sustained essential hypertension treated by the selective β_1 blocking agent bisoprolol. Blood pressure and heart rate significantly decreased after bisoprolol, whereas no significant change occurred in the diameter, the blood flow and in the vascular resistance of the carotid and brachial circulations. Pulse wave velocity significantly decreased in the brachioradial and the carotid femoral areas. The decrease in the latter was −1.6 ± 0.8 m/s with bisoprolol and −0.06 ± 0.80 m/s with placebo (p = 0.001). Brachial artery compliance significantly increased from 117 ± 49 to 205 ± 84 $cm^4 \cdot dynes^{-1} \cdot 10^9$ (p = 0.001), indicating that the antihypertensive effect of β_1 blockade is associated with an improvement in the viscoelastic properties of the brachial artery wall.

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Both clinical and experimental data[1,2] indicate that a nonselective β-blocking agent such as propranolol does not modify arterial compliance despite a significant blood pressure reduction. On the other hand, β-blocking agents with sympathomimetic activity have been shown to produce a slight increase in brachial artery diameter in hypertensive subjects.[3] Although such findings suggest that β-blocking drugs might have heterogeneous effects on the arterial system depending on their pharmacologic properties, no specific study was performed to investigate selective β blockade.

The selective β_1 blocking agent bisoprolol is known to have a high level of selectivity with a pharmacologic duration of action approximating 48 hours.[4,5] In the present, double-blind, crossover design, the effects of bisoprolol on the arterial system are studied in patients with sustained essential hypertension. Large arteries are investigated using noninvasive techniques involving pulsed Doppler flowmetry for the common carotid and the brachial arteries and determinations of pulse wave velocity.

METHODS

Patients: Fourteen patients with essential hypertension (7 men and 7 women, mean age ± 1 standard deviation 53 ± 8 years [range × 42 to 66]) completed this study. Mean weight and height were 73 ± 12 kg and 167 ± 9 cm, respectively. Diastolic pressure on mercury sphygmomanometer at the day of the inclusion was constantly >95 mm Hg after a 30-day placebo period. All subjects had mild to moderate hypertension according to World Health Organization criteria (90 mm Hg < diastolic blood pressure <115 mm Hg on mercury sphygmomanometer, Korotkoff phase V). Extensive clinical and biologic investigations were performed according to previously described procedures,[6,7] indicating that patients had essential hypertension with no cardiac, neurologic or renal involvement or arteriosclerosis obliterans of the legs, or diabetes mellitus. Patients gave written consent after a detailed description of the procedure.

The patients participated in an 8-week, randomized, double-blind, crossover study. After the placebo period, they were randomized into 2 groups. Subjects in group A received tablets containing 10 mg of bisoprolol daily

for 4 weeks. Subjects in group B received identical tablets containing placebo. At the end of this period, a crossover was made with patients in group A taking placebo and in group B taking active treatment for 4 weeks. Hemodynamic determinations were performed at the day of the inclusion and at the end of the first (fourth week) and the second (eighth week) periods.

Hemodynamic determinations: The study was performed at controlled room temperature of 20 ± 2.5 C, after 30 minutes of rest, with the subject in the recumbent position. Hemodynamic measurements were obtained before and 5 hours after the last administration of bisoprolol or placebo (fourth and eighth week), according to the well-known pharmacokinetic and pharmacodynamic effects of the drug.[4,5] Arterial blood pressure was measured automatically every 2 minutes in the left arm with an oscillometric blood pressure recorder (Dinamap, model 845 P, Critikon, Tampa, Florida). Hemodynamic measurements were performed first on the right common carotid artery, then on the right brachial artery within 15 minutes, during which blood pressure remained stable. No significant changes in blood pressure and heart rate occurred when the 2 periods were compared.

Carotid and forearm hemodynamic values were obtained with a bidimensional pulsed Doppler system[7] (Alvar Electronics, Montreuil, France), the probe of which was fixed with a stereotactic device over the course of the artery as previously described and validated.[6,7] This apparatus enabled the diameter and the blood velocity of the artery to be measured according to 2 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 2 transducers, which formed a 120° angle between them, so that when Doppler signals recorded by each transducer were equal in absolute value, the ultrasonic incidence with the vessel axis was 60°. 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. Methodology and reproducibility have been described in detail elsewhere.[6,7] Blood flow was calculated as the product of the blood velocity and cross-sectional area deduced from the arterial diameter by using a cylindrical representation of the artery. Arterial blood flow was expressed in millimeters per minute. Local vascular resistance (mm Hg·min·ml^{-1}) was calculated as the ratio between simultaneous mean blood pressure and mean blood flow.

For the determination of pulse wave velocity, 5 different Doppler flow recordings were obtained simultaneously at 5 sites[6,8]: at the base of the neck over the common carotid artery, over the right femoral artery,

over the right posterior tibial artery, over the right brachial artery in the axilla, and at the right radial artery at the wrist. Flow was measured with a nondirectional Doppler unit (SEGA M842 10 MHz) with handheld probes. Transcutaneous Doppler flow waves were recorded on a tape recorder at high speed (150 mm/s). Pulse wave velocity was determined as foot-to-foot wave velocity. The foot of the flow wave was identified as the point of the commencement at the sharp systolic upstroke. When this point could not be defined precisely, a tangent was drawn to the last part of the preceding flow wave and to the upstroke of the next wave, and the foot wave was taken as the point of intersection of these 2 lines. The time delay was measured between the feet of the flow waves recorded at these different points and the electrocardiographic signal recorder simultaneously. The average of ≥10 beats was taken as pulse transit time. The distance travelled by the pulse was measured over the surface of the body with a tape measure as the distance between the different recording sites. Arterial pulse wave velocity was calculated as the ratio between distance and transit time. The reproducibility of the measurements have been published in detail elsewhere.[6,8]

Brachial artery compliance was evaluated using a propagative model.[6,8,9] For large arteries, the most widely accepted relation between pulse wave velocity (PWV) and elastic modulus (E)[8] is given by the Moens Koeteweg equation:

$$PWV^2 = (Eh/2rp)$$

or by the Bramwell-Hill equation:

$$PWV^2 = (VdP/dV)$$

where E = Young's modulus of the wall, h = wall thickness, r = vessel radius, p = blood density, dV,dP = changes in volume (V) and pressure. As detailed elsewhere,[9] assuming a thin arterial wall, compliance of the brachial artery (expressed per unit length) may be calculated as: $dV/dP = 3.14 \ r^2/p \ PWV^2$.

Statistical evaluation[10]: Baseline values of groups A and B were compared with a 2-way analysis of variance and were not statistically different. Modifications of the different hemodynamic and biologic parameters were compared with a 3-way (patient, treatment, sequence) analysis of variance. This test did not indicate any difference in the 2 sequences of treatment. A p value <0.05 was considered significant.

RESULTS

Tables I, II and III summarize the mean value of blood pressure, heart rate, carotid and brachial arterial parameters and pulse wave velocity in the 3 conditions: baseline, after placebo and after active treatment.

After administration of bisoprolol, blood pressure and heart rate significantly decreased compared with placebo: systolic pressure, -17 ± 16 mm Hg (vs -6 ± 12 mm Hg; p = 0.03); diastolic pressure, -17 ± 12 mm Hg (vs -5 ± 10 mm Hg; p = 0.006); mean arterial pressure, -17 ± 13 mm Hg (vs -6 ± 11 mm Hg;

TABLE I Blood Pressure and Heart Rate

	Baseline	After Placebo	After Bisoprolol
Systolic blood pressure (mm Hg)	156 ± 15	148 ± 16	137 ± 18*
Diastolic blood pressure (mm Hg)	101 ± 5	94 ± 11	83 ± 12†
Mean blood pressure (mm Hg)	120 ± 7	112 ± 13	101 ± 14†
Heart rate (beats/min)	79 ± 12	77 ± 10	60 ± 11†

*p <0.05; †p <0.01; ‡p <0.001.
Values are mean ± 1 standard deviation.
The p value indicates the intergroup comparison between placebo and bisoprolol.

TABLE II Hemodynamic Parameters in Regional Circulations*

	Baseline	After Placebo	After Bisoprolol
Brachial artery			
Diameter (cm)	0.48 ± 0.06	0.47 ± 0.06	0.48 ± 0.05
Blood flow velocity (cm/s)	7 ± 4	6 ± 4	6 ± 2
Blood flow (ml/min)	81 ± 63	75 ± 55	64 ± 37
Resistance (mm Hg · min · ml⁻¹)	2.4 ± 1.6	2.3 ± 1.3	2.1 ± 1.2
Common carotid artery			
Diameter (cm)	0.61 ± 0.07	0.61 ± 0.06	0.61 ± 0.07
Blood flow velocity (cm/s)	17 ± 5	18 ± 5	16 ± 5
Blood flow (ml/min)	303 ± 107	314 ± 100	289 ± 103
Resistance (mm Hg · min/ml⁻¹)	0.47 ± 0.27	0.40 ± 0.17	0.41 ± 0.22

*No significant change was observed.
Values are mean ± 1 standard deviation.

p = 0.01). Similar changes were observed with heart rate: -20 ± 10 vs -4 ± 8 beats/min (p = 0.0001).

Significant changes in pulse wave velocity were observed after bisoprolol administration: -1.6 ± 0.8 vs -0.06 ± 0.80 m/s (p = 0.001) for carotid-femoral pulse wave velocity (Figure 1); -3.3 ± 2.4 m/s vs -0.3 ± 1.6 m/s (p = 0.001) for brachioradial pulse wave velocity; -1.3 ± 2.5 m/s vs -0.7 ± 1.6 m/s (difference not significant) for femorotibial pulse wave velocity.

No significant change in carotid and brachial hemodynamics were observed (Table II), except for brachial artery compliance which increased significantly after bisoprolol (205 ± 84 vs 117 ± 49 cm⁴·dynes⁻¹·10⁻⁹; p = 0.001) (Figure 2).

DISCUSSION

In the present investigation, the β_1 blocking agent bisoprolol was shown to greatly decrease blood pressure in patients with sustained essential hypertension.

The antihypertensive effect of β-blocking agents is usually attributed to a decrease in vascular resistance at

TABLE III Pulse Wave Velocity Determinations

	Baseline	After Placebo	After Bisoprolol
Pulse wave velocity (m/s)			
Carotid femoral	9.5 ± 1.4	9.4 ± 1.3	7.9 ± 0.9*
Brachioradial	12.8 ± 2.3	12.6 ± 2.7	9.7 ± 2.0*
Femorotibial	12.8 ± 2.7	12.1 ± 2.5	11.5 ± 2.9

*p <0.001.
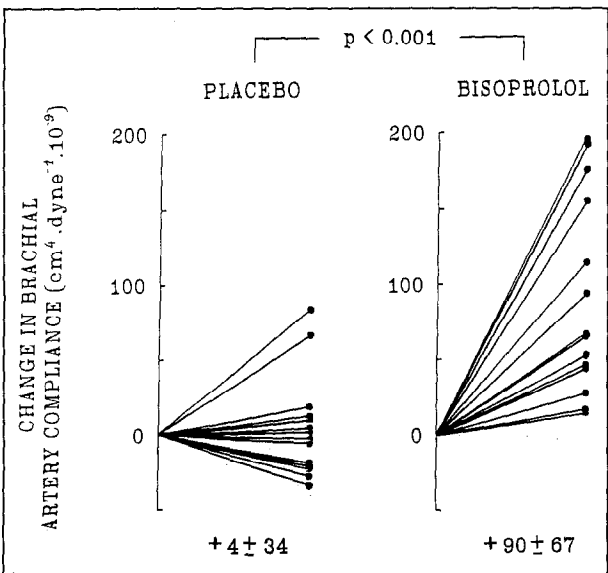Values are mean ± 1 standard deviation.

FIGURE 1. Changes in carotid femoral wave velocity after bisoprolol and placebo.
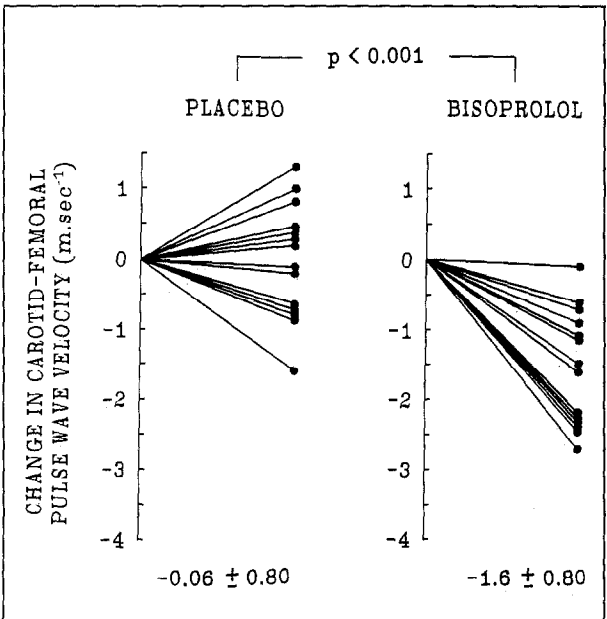

FIGURE 2. Changes in brachial artery compliance after bisoprolol and placebo.

any given value of cardiac output.[11] Because blood flow and vascular resistance were unchanged in the carotid and the brachial circulation after bisoprolol, the findings of our study support the hypothesis that arteriolar dilatation occurred in other regional circulations, as in the mesenteric or the renal areas.

Despite the significant reduction in blood pressure, there was no evidence of a passive change of the arterial diameter in the brachial and carotid circulation. Because blood flow velocity did not change, a flow-dependent mechanism could not explain the lack of change in arterial diameter.[12] Since diameter may be considered the same before and after blood pressure reduction, the result suggests that, after bisoprolol, a shift of the pressure-diameter curve occurred toward lower values in blood pressure.[9] However, the present pulsed Doppler method is known to have very precise limits for an adequate determination of internal diameter. The resolution of the method is directly related to the sample volume size and has been shown to approximate 0.035 cm.[7,13] In that condition, minor changes in arterial diameter may be present but remain outside the resolution limits of the method. This possibility appears likely with bisoprolol. Acute β_1 blockade by atenolol has been shown to cause a decrease in brachial artery diameter[14] and long-term bisoprolol to produce a decrease in abdominal aorta diameter[5] in patients with sustained essential hypertension. Since these drugs act on β_1 receptors with no effect on β_2 receptors, such findings may be attributed to the mechanical effect of the blood pressure reduction itself.

In contrast to the unchanged arterial diameter, bisoprolol produced a decrease in pulse wave velocity in the aortic, the brachioradial and the femorotibial areas. Only the changes observed in the aorta and the upper limbs were shown to be significant. Similar results have been observed with another β_1 blocking agent atenolol,[15] but not with metoprolol.[16] Reasons for this discrepancy are difficult to explain. More significant changes may be observed with crossover designs (as for atenolol and for our study) than with parallel group designs (as for metoprolol). Nevertheless, the decrease in pulse wave velocity with bisoprolol is compatible with the simple mechanical consequence of the blood pressure reduction itself.

The most important finding of the present study was the significant increase in arterial compliance observed in the brachial circulation. An increase in arterial compliance after β blockade has been noticed with β-blocking agents having ancillary properties such as pindolol or labetolol[3,17]; however, such compliance change has not been seen with noncardioselective β-blocking agents such as propranolol.[1,2] Whether such differences in vas-

cular properties are directly related to the role of β_2 receptors in the vasculature of hypertensive patients remains an open question and requires further investigations.

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