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EFFECT OF NITROGLYCERIN ON PERIPHERAL LARGE ARTERIES IN HYPERTENSION

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1 Blood pressure, systemic arterial compliance, and diameter, blood flow velocity, volumic flow and impedance of the brachial artery were measured before and after intravenous administration of nitroglycerin (15 μg/min during 15 min) in 11 patients with sustained essential hypertension.

2 For the evaluation of the diameter of the brachial artery, a bidimensional pulsed Doppler was used, enabling the angle of the ultrasound beam relative to the flowing stream of blood to be measured with an error of less than 2%.

3 After nitroglycerin, systolic pressure significantly decreased ($P < 0.01$) without significant change in diastolic and mean arterial pressures, cardiac index, stroke index and total peripheral resistance.

4 Systemic arterial compliance and brachial artery diameter significantly increased ($P < 0.001$; $P < 0.01$) while velocity and blood flow of the brachial artery were unchanged.

5 The pattern of the input impedance of the brachial artery was consistent with a predominant effect of nitroglycerin on the viscoelastic properties of peripheral large arteries.

6 The study provided evidence that, in hypertensive patients, nitroglycerin has a direct effect on peripheral large arteries, causing an increase in arterial diameter and compliance, thus leading to a predominant decrease in systolic pressure.

Introduction

Epidemiological studies have shown the contribution of systolic pressure as an independent risk factor in cardiovascular disease over 40 years (Kannel *et al.*, 1971). Since reduction of systolic pressure may be important to reduce morbidity and mortality, the use of vasodilating drugs acting predominantly on the systolic component of blood pressure might be of chief importance in cardiovascular pathology.

Nitroglycerin has been shown to effectively reduce systolic rather than diastolic pressure (Christensson *et al.*, 1969; Chrysant *et al.*, 1977). The most involved mechanism to explain the pressure decrease is the action of the drug on the venous system through venodilatation and decreased venous return, causing a reduction in stroke volume (Mason, 1978). However, it is known that the drug has also an early arterial response (Mason, 1978), which can be predominant on large arteries and contribute to the fall in systolic pressure: an increase in arterial compliance due to nitroglycerin might play an important role in the decrease in systolic pressure (Simon *et al.*, 1979a; Levenson *et al.*, 1980). However, little information has been obtained in clinical pharmacology, probably due to a lack of appropriate techniques.

In the present study, two methods were used to evaluate the physical properties of large arteries in hypertensives. Firstly, systemic arterial compliance have been estimated from analysis of the arterial pressure curve, using a simple viscoelastic model (Simon *et al.*, 1979a,b). Secondly, we have developed (Peronneau & Leger, 1969; Levenson *et al.*, 1981; Safar *et al.*, 1981), a pulsed Doppler velocimeter particularly suitable for the determination of blood flow in peripheral arteries. With the use of a double transducer probe, the angle of the ultrasound beam relative to the flowing stream of blood can be simply evaluated, enabling the arterial calibre to be estimated (Peronneau *et al.*, 1969; Levenson *et al.*, 1981; Safar *et al.*, 1981). In the present investigation, we have studied the mechanism of the decrease in systolic pressure caused by nitroglycerin in patients with sustained essential hypertension. Since the action of the drug given sublingually is rather short lasting and may differ qualitatively with time, nitroglycerin has

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been administered in a continuous intravenous infusion.

Methods

Patients

Eleven male hypertensive patients were included in the study. Mean age was 40 years (ranges: 26–58 years). Mean weight was 83 kg (ranges: 60–95 kg). The patients were hospitalized for a 6 day period on a 100 mEq/day sodium diet. Antihypertensive treatment was discontinued at least 4 weeks before the study. In all patients, diastolic blood pressure was equal to or higher than 90 mmHg on the third day of hospitalization. Before the study, a complete clinical and laboratory evaluation had been carried out, including physical examination, routine laboratory tests, determination of urinary catecholamines, measurements of plasma electrolytes, and times intravenous pyelography. All the patients were diagnosed as having moderate essential hypertension; creatinine clearance was normal (greater than 90 ml/min); the optic fundi showed no haemorrhages, exudates and/or papilloedema. None of the patients had clinical signs of congestive heart failure, coronary insufficiency, valvular heart disease, peripheral vascular 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.

Haemodynamic parameters and systemic arterial compliance

The haemodynamic study was performed in the 11 patients without premedication, after overnight fasting, on the third day of hospitalization. The room temperature was 20°–23° C. With the subject in the supine position, two transcutaneous catheters were inserted into the right and left antecubital veins, one for the injection of indocyanine green and the other for drug administration. The investigation began at least 30 min after insertion of the catheters.

Arterial pressure was recorded on a Thomson Telco apparatus via a metallic number 18 hypodermic needle inserted into a brachial artery. The needle was connected to a Statham P 23 db balanced resistive strain gauge via a special low compliance short 10 cm catheter of teflon regularly flushed with heparinized Ringer's fluid. No significant distortion existed in the recorded signal. The system was checked with both time and frequency-domaine measurements and showed a flat response beyond 80 Hz. Inspection on the oscilloscope of recorded curves over about 1 min of time permitted representative 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 (Simon *et al.*, 1979a). It was expressed in ml min^{-1} m^{-2} after correction for body surface area. The normal value of the laboratory between 25 and 45 years was 3535 ± 196 ml min^{-1} m^{-2}.

The procedure for the determination of systemic arterial compliance has been previously described and validated (Simon *et al.*, 1979b). Briefly, the arterial system can be treated as a simple RC model which associates in series a capacitive element (C) and a resistive element (R). Such a model discharges mono-exponentially as function of time, and the time constant (TCT) of the system, i.e. the reciprocal of the exponential slope discharge, represents the product of the capacitance (C) by the resistance (R):

$$TCT = C \times R$$

so that the compliance is calculated according to the formula $C = \frac{TCT}{R}$

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

$$TPR\ (mmHg\ ml^{-1}\ s^{-1}) = MAP/CO$$

where MAP is mean arterial pressure (mmHg) and CO cardiac output (ml/s). The TCT value was calculated from the pulse pressure curve recorders at speeds of 100 mm/s by correcting in semilogarithmic scale the pressure time curve during the last two third parts of the diastole. The correlation coefficient and the slope of the regression line were calculated. The reciprocal value of slope, or time-constant (TCT) 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 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 between 25 and 45 years was 1.26 ± 0.10 ml $mmHg^{-1}$ m^{-2}.

Arterial haemodynamics

Arterial haemodynamics of the brachial artery were performed in six patients using a bidimensional pulsed Doppler system, as previously described and validated (Peronneau *et al.*, 1974; Safar *et al.*, 1981; Levenson *et al.*, 1981). The zero-crossing velocimeter used in the study operates at a frequency of 8 mHz and has two original features: (i) the pulsed emission

is associated with an adjustable range-gated time system, and (ii) 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. Using adjustments of time delay and reception duration, 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 $d = c/2 \times t$, where c is the ultrasound speed in tissues and t the reception time. The 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 α 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 (Levenson *et al.*, 1981). The angle θ between each ultrasonic beam and the vessel axis is then equal to $\alpha/2$. In such conditions the error from the determination of angle θ is less then 2% (Levenson *et al.*, 1981). Once the correct position has been found, the probe can be fixed by means of a stereotaxis device placed around the arm. In a previous study (Levenson *et al.*, 1981), the accuracy of the Doppler determinations has been studied with a hydraulic test device using calibrated latex tubes. So, it has been shown that the overestimation of the arterial diameter due to the sample volume size was not significantly different from zero.

In clinical practice, subjects were examined in the supine position after a preliminary rest period of 20 min 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 loud speaker and recorded with a Siemens apparatus on paper. With the probe properly placed, 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 Δt 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/s) and θ the angle between the ultrasonic beam and the vessed axis. Cross-sectional blood velocity was measured with the time delay adjusted to the depth of the proximal wall of the artery and the duration reception to its diameter. The calibration voltage of the apparatus corresponded to a velocity of 38 cm/s for an incidence angle of 60°. Velocity was recorded at a paper speed of 50 mm/s. Mean velocity (Vm) was calculated by electronic integration of the velocity curve and was the mean value of 10 successive cardiac cycles for each transducer. The volumic flow (Q ml/min) was calculated according to the formula: $Q = \Pi D^2/4 \times Vm$. All determinations were repeated at least twice in each patient. The reproducibility was 8 ± 2% for the apparent echo Doppler diameter and 4 ± 2% for the mean velocity.

According to the above methods, pressure and velocity signals could be recorded simultaneously on a multichannel magnetic tape recorder enabling an evaluation of input impedance of the brachial artery. Pressure and flow measurements were studied during a haemodynamically stable period and were averaged from at least 10 consecutive beats over two respiratory cycles. These analogue signals were later digitized at a sampling interval of 10 ms by an analogue to digital converter. Data analysis was carried out on a programmable calculator (Hewlett Packard) which converted pressure and velocity data to Fourrier series, applied corrections for the measured mean arterial diameter and computed brachial impedance as functions of frequency (Nichols *et al.*, 1977). Input impedance modulus at each harmonic frequency was calculated by dividing flow modulus into pressure modulus, and impedance phase by subtracting the phase angle of flow from that of pressure (Nichols *et al.*, 1977). The impedance of 0 Hz or 'input resistance' was calculated by dividing mean flow by mean pressure. To avoid values that probably represent the noise levels of the measurement systems, the procedure eliminated all data above 10 Hz (Nichols *et al.*, 1977).

Administration of nitroglycerin

In all patients, the haemodynamic investigation was performed before and after intravenous infusion of nitroglycerin within 15 min. A stock solution of 1% nitroglycerin in absolute ethanol was used. This solution was diluted in 5% dextrose in water to give a final concentration of 60 μg nitroglycerin/ml and transferred into 250 ml serum vials. The vials were stored in refrigeration protected from light, and used within 6 months of preparation (Christensson *et al.*, 1969). The infusion of nitroglycerin was begun at 5 μg/min, using a Harvard pump. The rate of adminis-

tration was administered by stepwise at 5 min intervals. The mean dose was 15 μg/min (ranges : 5–20 μg/min). This low dose was chosen because : (i) no significant decrease in mean arterial pressure could be observed, and (ii) with such amount of nitroglycerin, the blood ethanol concentrations have no pharmacological effects (Christensson *et al.*, 1969).

Statistical methods

Means and standard deviations were calculated according to standard statistical methods (Draper & Smith, 1966). Differences in means before and after nitroglycerin were assessed by the paired *t*-test. A *P*-value of less than 0.05 was accepted as being statistically significant.

Results

Haemodynamic parameters and arterial compliance (Table 1)

After nitroglycerin administration, systolic pressure significantly decreased ($P < 0.01$) while mean and diastolic pressures remained unchanged. Heart rate increased ($P < 0.05$). Left ventricular ejection time, stroke index and cardiac index slightly but unsignificantly decreased. No change in total peripheral resistance was observed. Arterial compliance increased significantly from 0.89 ± 0.08 to 1.54 ± 0.21 ml $mmHg^{-1}\ m^{-2}$ ($P < 0.001$).

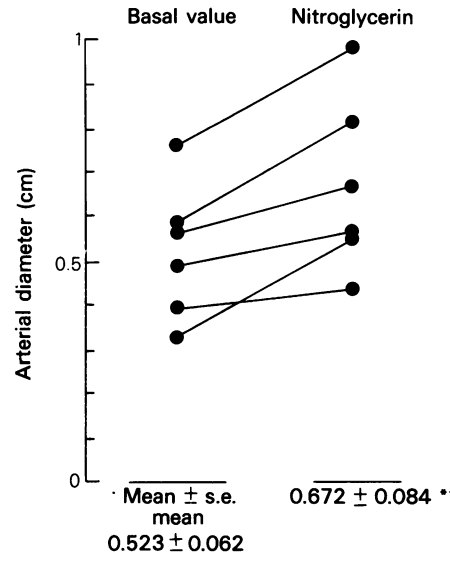

Figure 1 Increase in brachial arterial diameter produced by nitroglycerin (six patients). ** $P < 0.01$.

Diameter, velocity, blood flow and impedance of brachial artery

Figure 1 shows that nitroglycerin increased significantly the arterial diameter from 0.523 ± 0.062 to 0.672 ± 0.084 cm ($P < 0.01$). Velocity and blood flow were respectively 10.3 ± 3.74 cm/s and 145 ± 66

Table 1 Haemodynamic parameters ± 1 s.e. mean before and after nitroglycerin administration (11 patients).

	Control	*Nitroglycerin*
Systolic arterial pressure (mmHg)	165 ± 7	152 ± 6**
Diastolic arterial pressure (mmHg)	92 ± 3	94 ± 3
Mean arterial pressure (mmHg)	118 ± 4	113 ± 4
Heart rate (beats/min)	72 ± 3	76 ± 3*
Left ventricular ejection time (m/s)	334 ± 2	311 ± 2
Cardiac index (ml $min^{-1}\ m^{-2}$)	3407 ± 177	3175 ± 174
Stroke index (ml m^{-2})	48 ± 1	43 ± 2
Total peripheral resistance (dynes $s^{-1}\ cm^{-5}\ m^{-2}$)	2897 ± 202	2940 ± 156
Systemic arterial compliance ml $mmHg^{-1}\ m^{-2}$)	0.89 ± 0.08	1.54 ± 0.21***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

ml/min before nitroglycerin and 7.4 ± 1.15 cm/s and 164 ± 85 ml/mn after nitroglycerin. These changes were not significant.

Figure 2 illustrates the modifications in brachial input impedance observed after nitroglycerin in administration. For harmonics 1, 2, 3, 4, and 5, the moduli decreased significantly. Although the inflexion point was shifted on the right, no significant change was observed in the phases (Figure 2).

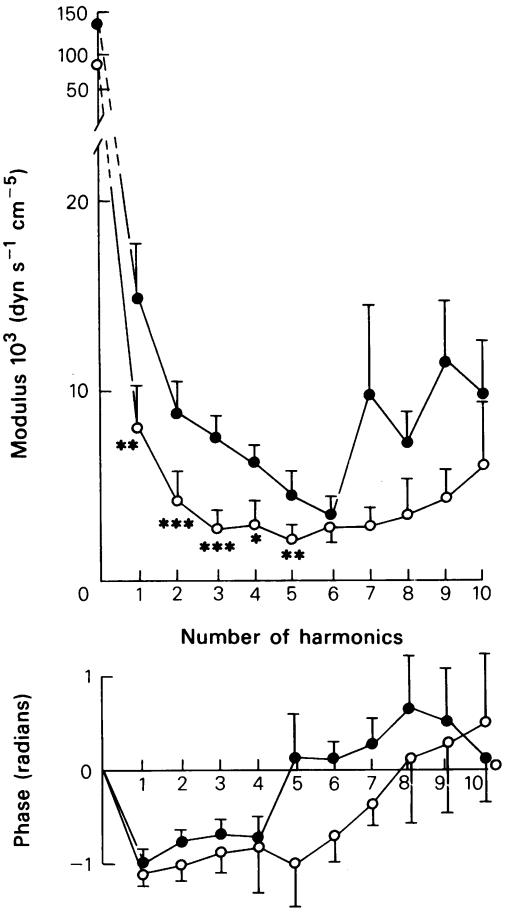

Figure 2 Arterial impedance of the brachial artery before (○) and after (●) nitroglycerin administration (six patients). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Discussion

It is well known that systolic pressure is mainly determined by the left ventricular stroke volume, the peak rate of ejection and the distensibility of the arterial walls. In previous reports, the reduction in systolic pressure produced by nitroglycerin was presumably attributed to the decrease in stroke volume, through peripheral venous pooling and decreased venous return to the heart (Mason, 1978). In the present study, insignificant changes in stroke volume index and left ventricular ejection were observed, minimizing the role of an altered ventricular ejection in the mechanism of the decrease in systolic pressure. In contrast, profound nitroglycerin-induced changes in peripheral arteries were shown and can be taken into consideration in the analysis of the systolic reduction.

The more consistent finding after nitroglycerin administration was the increase in arterial compliance and in arterial diameter. Since low doses of nitroglycerin were used (Christensson *et al.*, 1969), mean blood pressure did not change significantly. Thus, the increase in arterial compliance could not relate to the mechanical effect of the blood pressure reduction. On the other hand, the increase in arterial diameter could not be related to a translation of blood volume from the venous to the arterial compartment of the circulation: the lack of change in stroke volume, left ventricular ejection time and total peripheral resistance exclude this possibility. Thus, the increase in arterial diameter and compliance after nitroglycerin points to a direct vasodilating effect of the drug on peripheral large arteries. This interpretation is consistent with (i) the dislocation or even loss of the dicrotic notch induced by nitroglycerin in the brachial artery (Ferrer *et al.*, 1966) and (ii) the preferential action of the drug on the larger rather than the smaller coronary arteries (Schnaar & Sparks, 1972; Harder *et al.*, 1979; Cohen & Kirk, 1973).

In the present study, a more complete description of the nitroglycerin effects was given by the input impedance spectrum of the brachial artery. After nitroglycerin, the whole curve was flatter than the control curve, with a significant reduction in the low frequencies impedance moduli. In addition, in the phases, the inflexion point was shifted on the right. This pattern is also consistent with important changes in the viscoelastic properties of the arterial wall caused by nitroglycerin (Nichols *et al.*, 1977).

In conclusion, the present study has emphasized the predominant vasodilating effect of nitroglycerin on peripheral large arteries. In patients with sustained hypertension, nitroglycerin induced a predominant decrease in systolic pressure, related to an increase in arterial compliance and diameter. Such observations could be relevant for further investigations about the clinical pharmacology of nitroglycerin-like drugs in man.

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