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Baroreflex Response and Vasodilating Drugs in Essential Hypertension*

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Blood pressure, heart rate, and arterial diameter of the brachial artery were studied in patients with sustained essential hypertension before and after administration of three vasodilating drugs: dihydralazine, diltiazem, and dinitrate isosorbide (ISDN). The diameter of the brachial artery was measured using a pulsed Doppler device, enabling the angle between the ultrasound beam and the vessel axis to be evaluated with a precision inferior to 2 percent. The three drugs had similar effects in decreasing the blood pressure and the forearm vascular resistance. Dihydralazine reduced the arterial diameter (p<0.001) and increased heart rate. Diltiazem and ISDN increased markedly the arterial diameter (p<0.001) but did not change heart rate. Dihydralazine decreased the tangential tension of the arterial wall, while diltiazem and ISDN did not. The study provided evidence that, with vasodilating drugs, the changes in the caliber of peripheral large arteries, which are a determinant of wall arterial tension, can influence the baroreflex-mediated tachycardia caused by the use of the drugs.

Several indices of the baroreflex function have been proposed in man. In most studies, transient modifications of intra-arterial blood pressure are obtained by administration of vasoactive substances, causing an activation of the baroreflex response and the expected consequences on heart rate and peripheral resistance. In some studies, local modifications of pressure are obtained within a neck chamber apparatus.

All of these methods are based on the assumption that the pressure is the exclusive determinant of the baroreflex mechanisms. However, it is not the pressure per se but the distortion of the arterial wall which activates the baroreflex response. This observation suggests that an evaluation of the diameter of peripheral arteries is necessary to investigate the baroreflex function in man.

We recently developed a new pulsed Doppler device enabling the diameter of peripheral large arteries to be determined with an error of less than 10 percent. In the present study, we applied this methodology to the evaluation of arterial diameter before and after administration of three vasodilating drugs causing a possible baroreflex response: diltiazem, a calcium inhibitor; isosorbide dinitrate (ISDN), a nitroglycerine-like substance; and the classic drug dihydralazine whose data have been published previously.

MATERIAL AND METHODS

Thirty-eight male hypertensive patients were included in the study. Mean age was 43 ± 4 years (± 1 SEM), mean weight was 78 ± 3 kg, and mean height 173 ± 2 cm. The patients were hospitalized for a six-day period receiving a 100 mg/day sodium diet. Antihypertensive treatment was discontinued at least four weeks before the study. In all patients, diastolic blood pressure was equal to or higher than 90 mm Hg on the third day of hospitalization. On the basis of usual investigations, all the patients received diagnoses of moderate uncomplicated essential hypertension, grade 2. From the 38 patients, 11 were investigated before and after administration of dihydralazine, 16 before and after administration of diltiazem, and 11 before and after administration of isosorbide dinitrate (ISDN). Their mean age was, respectively, 43 ± 3, 45 ± 3, and 45 ± 4 years. The individuals included in each subgroup were never the same. The protocol was approved by INSERM (Institut National de la Santé et de la Recherche Médicale). Informed consent for the investigation was obtained from the patients after a detailed description of the
procedure.

After overnight fasting, the patients were brought to the hemo-
dynamic laboratory without premedication, and the study was
performed after 45 minutes of rest. Throughout the investiga-
tion, blood pressure was measured using a mercury sphygmomanometer,
and the abolition of Korotkoff’s sounds was used to determine
diastolic pressure. Heart rate was evaluated from the RR interval of
the ECG. Arterial diameter (D) and blood flow velocity (Vm) of
the brachial artery were measured using a bidimensional pulsed Dop-
pler system, as previously described and validated. Brachial blood
flow (Q mL/min) was calculated according to the following formula:

\[
Q = \frac{D^4}{16}\pi \times Vm.
\]

The vascular resistance was the ratio between mean arterial pressure and brachial blood flow (Q). Tangential
tension (T) of the brachial artery was calculated according to the law
of Laplace and the change in tension (\(\Delta T\)) was the difference in
tangential tension before and after drug administration.

Each vasodilating drug was infused to obtain a 15 to 20 percent
decrease in mean arterial pressure. For dihydralazine, the hemo-
dynamic study was performed before and 25 minutes after intra-
venous (IV) administration of 0.1 mg/kg dihydralazine. For diltiazem, the IV administration included a bolus injection of 0.2 mg/
kg followed by a perfusion of 0.1 mg/kg during 25 minutes, and the arterial hemodynamic studies were performed before and just after the perfusion was stopped (25 minutes). For isosorbide dinitrate, an IV administration of 0.90 mg/kg/min within 25 minutes was used.

Usual statistical evaluations were performed.

RESULTS

Dihydralazine decreased significantly systolic and dia-
stolic blood pressures from 177 ± 10/94 ± 7 to 158 ± 10/77 ± 6
mm Hg (p<0.001; p<0.01). Heart rate increased from 73 ± 3
to 96 ± 5 beats/min. The arterial diameter decreased signifi-
cantly (0.471 ± 0.02 vs. 0.503 ± 0.031 cm; p<0.001), while
brachial blood flow did not change significantly (106 ± 23 vs
100 ± 20 mL/min). Forearm vascular resistance decreased
from 72 ± 16 to 57 ± 11 mm Hg/mL/sec (p<0.05).

After diltiazem administration, blood pressure decreased significantly from 181 ± 5/90 ± 4 to 157 ± 5/82 ± 4 mm Hg
(p<0.001), while heart rate did not change (74 ± 4 vs 70 ± 3
beats/min). The arterial diameter increased greatly from
0.478 ± 0.021 to 0.526 ± 0.024 cm (p<0.01). Brachial blood
flow increased significantly (154 ± 15 vs 126 ± 9 mL/min;
(p<0.01), while forearm vascular resistance decreased from
63 ± 7 to 46 ± 5 mm Hg/mL/sec (p<0.01).

After ISDN administration, blood pressure decreased significantly from 190 ± 7/98 ± 7 to 175 ± 8/94 ± 7 mm Hg
(p<0.001; p<0.01), and heart rate was unchanged (79 ± 3
vs 76 ± 3 beats/min). The arterial diameter increased from
0.507 ± 0.016 to 0.562 ± 0.017 cm (p<0.01). Brachial blood
flow was unchanged (67 ± 16 vs 69 ± 16 mL/min). Forearm
vascular resistance decreased from 79 ± 4 to 67 ± 3 mm
Hg/mL/sec (p<0.02).

Only dihydralazine decreased tangential tension
(\(\Delta T = -5.3 ± 0.02 \) mm Hg/cm; p<0.001), while diltiazem
and ISDN had no significant effect (\(\Delta T\) was, respectively,
-0.01 ± 0.02 and +0.2 ± 0.03 mm Hg/cm).

COMMENTS

In the present study, use of the three vasodilating drugs
dihydralazine, diltiazem, and ISDN produced similar
decreases in blood pressure. The decrease was due to a
dilatation of small arteries, as indirectly suggested by the
calculation of forearm vascular resistance. However, the

three drugs had different effects on heart rate and peripheral large arteries.

After dihydralazine administration, the caliber of the
brachial artery decreased significantly. The reduction of the
arterial diameter could be due either to the mechanical effect
of the decrease in blood pressure or to the activation of the
autonomic nervous system usually observed with dihydral-
azine. However, the association of decreased forearm resistance
and reduced arterial diameter suggests that
dihydralazine has a preferential action on small rather than
on large arteries. On the other hand, diltiazem and ISDN
notably increased the arterial diameter of the brachial artery.
Since the increase occurred for the same antihypertensive effect as dihydralazine, the observed dilatation indicated a
direct effect of diltiazem and ISDN on peripheral large
arteries, in addition to their effect on small arteries.

With similar actions on blood pressure, the three
vasodilating drugs had different effects on the arterial wall
tension. The change in tangential tension was significant with dihydralazine but not with diltiazem and ISDN. Since it
is not the pressure per se but rather the distortion of
the arterial wall which activates the baroreflex function, such
an observation can be relevant for the interpretation of the
baroreflex-mediated tachycardia observed after vasodilata-
tion.

After dihydralazine administration, there was a decrease in
tangential tension due to the reduction in the arterial diameter. Obviously, the decrease in arterial wall tension participates in the maintenance of the baroreflex response and in the sustained increase in heart rate observed with dihydralazine. On the other hand, after giving diltiazem and ISDN, the direct effect of the drugs on peripheral large arteries possibly explains the lack of change in tangential tension and, therefore, the lack of tachycardia. This
interpretation agrees with two previous observations concern-
ing dihydralazine and diltiazem: (1) after IV administration of
diltiazem, a baroreflex response can be observed but disappears five minutes after the beginning of the perfusion, and (2) in a population of hypertensive patients given either
diltiazem or dihydralazine, a significant correlation can be
observed between the change in tangential tension and the
change in heart rate.

In the present study, the effect of vasodilating drugs on
peripheral large arteries cannot explain exclusively the lack
of tachycardia observed after vasodilatation. Additional
mechanisms can be proposed, such as the venous effect of the
nitroglycerin-like drugs on cardiopulmonary receptors and the
peculiar action of diltiazem on sinoatrial and atrio-
ventricular nodes. However, our findings emphasize the
role of the changes in arterial diameter for the activation of
arterial baroreceptors in man. This role might explain the
lack of tachycardia observed after administration of several
vasodilating drugs, such as the inhibitors of the renin-
angiotensin system. On the other hand, unexpected
changes in arterial diameter could obscure the interpretation of
several tests used for the evaluation of the baroreflex
sensitivity, such as the vasodepressor effect of nitroglycerin and
the vascular effects of the neck chamber suction.
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**Effects of Oral Clonidine on Baroreflex Function in Patients with Essential Hypertension**

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Clonidine reduces arterial blood pressure and heart rate by actions within the CNS. The mechanism appears to involve a net reduction of sympathetic outflow involving complex actions of clonidine within the anterior and posterior hypothalamus and medulla to permit increased inhibitory nerve traffic from the nucleus tractus solitarius to the medullary vasomotor center, and parallel enhancement of the vagal cardiac reflex. Since the nucleus tractus solitarius receives baroreflex afferent input from both the carotid sinus and aortic arch, clonidine might be expected to modulate baroreflex function, and several reports have indicated that intravenous (IV) clonidine does potentiate this reflex. We examined the effects of clonidine when given orally for a prolonged period to patients with mild to moderately severe essential hypertension, and we assessed its influence on baroreflex sensitivity for heart rate.

**MATERIALS AND METHODS**

We studied 30 patients aged 26 to 61 years with mild to moderately severe essential hypertension diagnosed by conventional criteria. We studied them following the withdrawal of previous antihypertensive medications and after they had received a placebo for three weeks. Following an overnight fast and after 45 minutes of sustained recumbent posture, we collected plasma for later measurement of catecholamines by a radioenzymatic assay.

We then measured baroreflex sensitivity by the regression of indirect systolic blood pressure responses, using a Beckman R-511 electrophysmograph, and the succeeding pulse intervals after small bolus injections of phenylephrine at approximately three-minute intervals, similar to the method of Smyth et al. We then gave our patients clonidine in divided doses of 0.2 to 0.4 mg/day, sufficient to reduce their diastolic blood pressures by 10 percent from baseline over the subsequent six to eight weeks. We repeated the study techniques two hours after the last dose of clonidine.

**RESULTS**

The effects of long-term oral clonidine are shown in Table 1. Clonidine produced significant decrements in both systolic and diastolic blood pressure, pulse rates, and plasma norepinephrine and epinephrine levels. In addition, we saw increased sensitivity to the pressor effects of small amounts of phenylephrine (reduced PD0) without a significant change in sensitivity to isoproterenol (CD50). The mean baroreflex slope increased by 78 percent, and baroreflex slope increased in 26 of 30 patients after clonidine treatment (Fig 1).

**DISCUSSION**

Clonidine produced concomitant reductions in blood pressure.