Peripheral Large Arteries and the Response to Antihypertensive Treatment

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SUMMARY Since systolic pressure is governed by the rate of ventricular ejection and the rigidity of the aortic wall, antihypertensive agents may have different effects on systolic and diastolic pressure. Despite an adequate decrease in diastolic pressure, systolic pressure may remain elevated due to structural alterations of large arteries. In the present study, a procedure is described to distinguish the dilation of small and large arteries. The former is evaluated from the calculation of forearm resistance and the latter from the determination of the arterial diameter of the brachial artery, using a bidimensional pulsed Doppler system. Nitroglycerin dilates the brachial artery, with no change in forearm resistance. Dihydralazine reduces the diameter of the brachial artery but decreases forearm resistance. Only calcium and converting-enzyme inhibitors dilate both small and large arteries and cause an increase in brachial blood flow. (Hypertension 5 (supp III): III-63-III-68, 1983)

Key Words • essential hypertension • pulsed Doppler • vasodilating drugs

In patients with uncomplicated sustained essential hypertension, the effectiveness of antihypertensive therapy is well established. In younger subjects, diuretics, beta-blocking drugs, or their combination improve about 75% of the patients.1 However, the decrease in cardiovascular morbidity and mortality is mainly due to a lower frequency of congestive heart failure, cerebrovascular hemorrhages, and rupture of abdominal aneurysm, which are directly related to the level of blood pressure. In contrast, the improvement of arterial disease, such as atherosclerotic coronary disease, which is often associated with hypertension, remains less obvious, particularly in older patients.

On the basis of experimental2 and clinical3 studies, it has been shown that, during the evolution of hypertension, an arterial disease may develop. The arterial lesions are not restricted to arterioles but involve also large arteries. In the latter case, increased diameter and thickness of the arterial wall and decreased arterial compliance unrelated to the level of blood pressure have been observed. Further, several epidemiological observations of mild hypertension4-6 suggest the importance of disease of the large arteries in hypertension: 1) antihypertensive treatment of mild hypertension is effective only in patients over 50 years; 2) the decrease in cardiovascular morbidity and mortality due to ischemic disease is much more pronounced than it would be expected from the observed slight decrease in blood pressure; and 3) when dead and surviving patients are compared, for the same level of diastolic pressure, systolic pressure is significantly higher in dead patients (M. Mooser, personal communication). Similarly, it has been found in subjects over 50 years that systolic pressure is a higher risk factor for cardiovascular morbidity and mortality than diastolic pressure.9 Further, increased systolic pressure is a good indirect marker of decreased compliance of large arteries in old subjects.10 Thus, in older hypertensives, the cardiovascular morbidity and mortality is not influenced exclusively by the level of pressure but also by the underlying disease of large arteries.

From these observations, it is obvious that a better knowledge of the lesions of large arteries is required in hypertensives to treat high blood pressure and the arterial disease simultaneously. In addition, a prospective study of the action of the different vasodilating drugs on large arteries would be extremely beneficial for the treatment of hypertension associated with atherosclerotic disease.

In hypertension, vasodilating drugs are commonly classified as acting on arterioles, on veins, or on both.11 The interest of this classification has been based on the specific consequences of a given vasodilator on cardiac function. For instance, in hypertension, only drugs acting on both the venous and the arteriolar sides of the circulation may decrease total peripheral resistance without significant change in cardiac output. However, this classification does not take into account the possible specific action of vasodilating drugs on large arteries. Although some animal experiments have shown that vasodilating drugs may have different effects on small and large arteries,12,13 no extensive study has been performed in humans, probably due to the lack of appropriate methodology.
Recently, new pulsed Doppler systems have been developed for better investigation of peripheral large arteries in humans.\textsuperscript{3,14} The present paper is devoted to this subject. A particular attempt has been made to distinguish in the vasodilating effect of the action on small and large arteries.

**Pulsed Doppler and the Problem of the Caliber of Small and Large Arteries**

**Hemodynamics of Peripheral Large Arteries in Humans**

Measures of peripheral arterial hemodynamics in humans have been made chiefly on the brachial and the common carotid arteries using a new bidimensional pulsed Doppler system.\textsuperscript{3,14} For this, a zero-crossing velocimeter has been used. The apparatus operates at a frequency of 8 MHz and has 2 novel 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 angle of observation between the ultrasonic beam and the axis of the blood column.

Briefly, each of the two transducers acts alternately 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 0.5 μsec. 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 $d = c/2 \times t$, where c is the ultrasound speed in tissues and t the reception time. The time delay and the reception duration 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 (fig. 1). The probe contains two transducers set at a known angle $\alpha$, one to the other; in the present system, this is 120°. Probe position is adjusted until two successive velocities, one from each transducer, are equal in absolute value.\textsuperscript{14} The angle 0 between each ultrasonic beam and the vessel axis is then equal to $\alpha/2$. In such conditions, the error from the determinations of angle $\alpha$ is less than 2%.\textsuperscript{14} Once the correct position has been found, the probe can be fixed by means of a stereotaxis device placed around the arm. The accuracy of the Doppler determinations has been studied with a hydraulic test device using calibrated latex tubes.\textsuperscript{14} 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 not significantly different from zero.

Cross-sectional blood velocity can be measured with the time delay adjusted to the depth of the proximal wall of the artery and the duration reception to its diameter. Mean velocity ($V_m$) is measured by electronic integration of the velocity curve, using the mean value of 10 successive cardiac cycles for each transducer. The reproducibility is 8% ± 2% for the apparent echo Doppler diameter and 4% ± 2% for the mean velocity.\textsuperscript{15} The volumic flow ($Q$ ml/min) is calculated according to the formula $Q = \pi D^2/4 \times V_m$.

**Vascular Resistance as an Evaluation of the Dilation of the Small Arteries**

Using the described pulsed Doppler system, we can calculate the forearm resistance as the ratio between mean arterial pressure (MAP) and brachial blood flow. As shown by studies of the impedance spectra,\textsuperscript{16} calculation of vascular resistance is useful, not as an exact quantitative indication of the physical properties of a vascular system but rather as a qualitative guide to the caliber of the small vessels. During the physiological adjustments, the two other components of the Poiseuille's law, i.e., blood viscosity and length of blood vessels, remain within the same range. Consequently, it is virtually safe to conclude that the lumen of some vessels in the bed has diminished. Milnor\textsuperscript{17} has recently summarized certain specific rules to be kept in mind for the interpretation of the changes in resistance; 1) these changes do not indicate which vessels have constricted or dilated and, in particular, they do not rule out the possibility of dilation of some vessels and con-
Arterial Diameter as an Evaluation of Dilation of Peripheral Large Arteries in Hypertension

Vasodilating drugs are usually considered as acting predominantly on small arteries. According to this concept, large arteries have a passive behavior. Thus, it is important to analyze the mechanical consequences on peripheral large arteries of a vasodilator causing both a dilation of arterioles and a decrease in MAP. For simplicity, the description will be restricted to the hemodynamic analysis in the time domain.

Two passive consequences result from the dilation of small arteries. First, there is a decrease in the diameter of peripheral large arteries, possibly due to the mechanical effect of the decrease in pressure and/or to the activation of the baroreflex mechanisms as a consequence of the blood pressure reduction. Second, according to the Hallock and Benson experiments, any decrease in pressure may cause an increase in arterial compliance, i.e., the ratio of the change in volume and the change in pressure in the artery. Since, in this example, the increase in arterial compliance is passive, a proportional decrease in systolic and diastolic pressure results from a primary dilation of small arteries.

From these observations, it appears that dilation of small arteries can induce three passive effects on large arteries: 1) a proportional decrease in systolic and diastolic pressures; 2) an increase in arterial compliance; and 3) a reduction in the arterial diameter and volume. Obviously, the active effect of any vasodilator on large arteries must be evaluated within this framework; any modification in the three mechanical consequences described may indicate a peculiar action of a given vasodilating drug on large arteries.

Indices of the Viscoelastic Properties of Large Arteries in Humans

In addition to the arterial diameter, the pulsed Doppler system enables the estimation of several indices of the viscoelastic properties of large arteries in humans.

Arterial Compliance and Distensibility

For the study of large arteries, the importance of arterial compliance must be stressed. In physiological conditions, large arteries have viscoelastic properties and play the role of a hydraulic filter. Due to the damping effect of large arteries, the periodic flow of the heart is changed into a continuous flow at the capillary level. Based on this concept, arterial compliance is a quantitative evaluation of the elasticity of large arteries. In clinical investigation, compliance of the brachial artery can be evaluated from a simple Windkessel first-order model of the circulation deduced from the Doppler system.

Arterial compliance, which is the slope of the non-linear relationship between pressure and volume inside the arteries, is not exclusively influenced by the level of blood pressure. Any change in the structural and/or functional characteristics of the arterial wall may change the pressure-volume curve and therefore modify arterial compliance independently of the level of blood pressure. On the other hand, it is well accepted that systolic pressure is governed by two dominant parameters, the rate of the ventricular ejection and the degree of arterial compliance. For a given ventricular ejection, a decrease in arterial compliance may cause an increase in systolic pressure, as observed in older subjects with systolic hypertension. Thus, any drug increasing arterial compliance by a direct effect on the arterial wall may decrease selectively systolic pressure, thus causing a nonproportional decrease in systolic and diastolic pressures.

In the case of passive behavior of the large arteries, we have seen that an inverse relationship between arterial diameter and compliance must be expected; the lower the pressure, the lower the arterial diameter and the higher the compliance. However, a physiological or pharmacological agent acting directly on the arterial wall may disrupt such a relationship. This possibility can be expressed quantitatively by the evaluation of arterial distensibility, i.e., the ratio between arterial compliance and arterial volume. In clinical investigation, arterial distensibility can be estimated independent of arterial compliance and arterial diameter, and volume from the determination of pulse wave velocity.

Peripheral Blood Flow

In a hydraulic system with cylindrical tubes in series and a constant flow, an increase in the diameter of a given tube is associated with a decrease in velocity, so that the flow remains within the same range. From this it follows that, in the circulation, when a pharmacological agent increases the arterial diameter, the observation of a concomitant increase in peripheral blood flow requires an elevation of blood flow velocity. Blood flow velocity is influenced by two dominant factors: 1) a backward factor, the resistance, i.e., the degree of dilation of the small arteries; and 2) an upward factor, the product of cardiac output by total peripheral resistance, which determines the pressure gradient. Thus, blood flow velocity in a regional artery, such as the brachial artery, is mainly influenced by the dilation of the small arteries and the activity of the cardiac pump.

Tangential Tension of the Arterial Wall

According to the Laplace law, tangential tension of the arterial wall equals the product of MAP and the radius of the artery. Any primary decrease in pressure will cause a decrease in arterial wall tension due both to the blood pressure reduction and to the de-
crease in arterial diameter. However, if a given vasodilating drug causes both a decrease in pressure and an increase in the diameter of large arteries, tangential tension will be maintained or slightly reduced. Such a possibility can be easily demonstrated in acute conditions. However, in long-term clinical studies, the changes in arterial wall tension are more difficult to calculate, since the thickness of the vessel also interferes with the viscoelastic properties of the arterial wall.2

Shear Stress
The importance of mechanical factors in the development of atherosclerosis has been studied extensively.19 Mechanical factors may operate by altering stresses in the vessel wall or rather at the vascular interface. The latter case is represented by shear stress, which is related to blood flow and not to arterial pressure. As is well known,17 shear stress is proportional to blood flow velocity and inversely related to the radius of the artery. It represents the viscous drag on endothelial cells and thus the forces tending to damage or dislodge them.

Effect of Vasodilators on Peripheral Large Arteries
Most of the effects of vasodilating drugs on peripheral large arteries have been studied in the brachial artery and, in some cases, in the common carotid artery.3–14

Dihydralazine
The classical drug, dihydralazine, exhibits several peculiar effects on peripheral large arteries. While the drug dilates the small arteries, causing a decrease in forearm resistance, the diameter of the brachial artery is reduced.3 The reduction is proportional to the decrease in blood pressure.3 Thus, in agreement with pharmacological studies,22 dihydralazine dilates chiefly the small arteries, with a minimal direct effect on large arteries. In the brachial artery, the decrease in arterial diameter is not associated with an increase in blood flow velocity.3 Peripheral blood flow is unchanged and contrasts with the increase in cardiac output. Finally, in acute conditions, arterial wall tension is significantly reduced.24 This change could either determine the baroreflex response or potentiate the reflex. In both cases, the reduction in arterial wall tension and diameter may contribute to the increase in heart rate commonly observed.

Nitroglycerin
Several studies have previously emphasized the venous effects of nitroglycerin [for review, (see ref. 11)]. In fact, the drug has also an early arterial effect,12 which is composed of several puzzling factors. First, there is dilation of the large arteries (fig. 1), which predominates over dilation of arterioles. The pattern has been recognized both in the peripheral large arteries14 and in the coronary arteries.12,13 Second, the in
crease in arterial diameter is accompanied by a decrease in blood flow velocity, so that no change in peripheral blood flow is observed. 24, 25, 26 Third, when low doses are used, the drug is able to increase the arterial compliance, but has no significant effect on ventricular ejection and total peripheral resistance. 25, 26 Finally, the drug decreases the blood pressure, but the decrease in systolic pressure predominates over the decrease in diastolic pressure. 25, 26 Since ventricular ejection is practically unchanged with low doses, the decrease in systolic pressure cannot be explained exclusively by the venous effects of the drug 11 and undoubtedly involves the increase in arterial compliance. Thus, at least in acute conditions, nitroglycerin and nitroglycerin-like drugs, such as sodium nitroprusside 19 and isosorbide dinitrate, 27 can be effective in the treatment of systolic hypertension in the elderly. 10

Calcium Inhibitors

In contrast with dihydralazine and nitroglycerin, the two calcium-inhibitor compounds, nifedipine and diltiazem, dilate small and large peripheral arteries equally. 24, 28 Since blood flow velocity is unchanged or increased, peripheral blood flow is markedly increased. This pattern is observed mainly with nifedipine. 24, 28 Arterial compliance seems to be elevated more than it could be expected from the simple decrease in blood pressure. 28

Both nifedipine and diltiazem induce a baroreflex-mediated tachycardia. However, in the case of diltiazem, the baroreflex response is transient and disappears 10 minutes after the beginning of the intravenous injection. 24 The increase in arterial diameter, which favors the lack of change in arterial wall tension, could possibly explain the disappearance of tachycardia. 24 With nifedipine, a more sustained increase in heart rate is observed. However, the drop in blood pressure is more important and rapid than with diltiazem, causing complex interactions between the neurotransmitter release and the calcium inhibition. 25, 26 The use of nifedipine with long-term effects on blood pressure could further modify this problem

Renin-Angiotensin Inhibitors

As for calcium inhibitors, captopril and MK 421 dilate both the small and the peripheral large arteries. 20, 22 The dilation of the large arteries can be observed even in the absence of a significant decrease in blood pressure (fig. 2). 26 Peripheral blood flow is increased both during short-term 20 and long-term treatment. 21, 22 contrasting with the lack of change in cardiac output. 23 Tangential tension is practically unchanged and could play a role in the mechanism of the unchanged heart rate. 34

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