DEPENDENCE OF VASODILATOR EFFECT OF DRUGS ON INITIAL DISTENSIBILITY OF THE VASCULAR BED

A. V. Syrenskii, B. G. Bershadskii, and V. A. Tsyrlin

UDC 615.225.2.015.4.036.8

KEY WORDS: vascular resistance; flow characteristics; vasodilator drugs.

Experimental and clinical observations have shown that the fall of blood pressure induced by drugs may be accompanied by opposite changes of vascular resistance [1-3, 8]. There is some evidence [1, 3, 5, 8] to suggest that changes in the vascular resistance to the blood flow caused by drugs depend on the initial functional state of the circulatory system. We know [6] that one of the main parameters of the functional state of arteries is their distensibility, which can be evaluated by analyzing the static flow–pressure curves, which in the Soviet literature have been called "flow characteristics" [7]. However, no direct experimental data have been obtained to show relations between the effect of vasodilator drugs and the initial distensibility of the vessels.

The aim of this investigation was to quantify distensibility of the blood vessels and to reveal the relationship between distensibility of arteries and the action of certain vasodilator drugs.

EXPERIMENTAL METHOD

Altogether 25 experiments were conducted on anesthetized (urethane 800 mg/kg, sodium hydroxybutyrate 800 mg/kg), curarized cats with artificial ventilation of the lungs. The systematic circulation was perfused by the method in [4], with the natural circulation and oxygenation of the blood maintained in the pulmonary circulation. To determine the flow characteristics, stepwise changes in the perfusion volume (Q) were produced and the levels of perfusion pressure when stabilized after 1-3 min were recorded with an electromanometer (P). Perfusion volumes were chosen within a range such that the corresponding values of perfusion pressure in the initial state of the animals varied between 70 and 130 mm Hg. The flow characteristics were determined before and after intravenous injection of papaverine (2 mg/kg), phentolamine (1 mg/kg), and dihydroergotamine (0.5 mg/kg).

The flow characteristics were approximated by means of the power function:

$$Q=\beta P^{\alpha} \quad \text{or} \quad \lg Q=\lg \beta+\alpha \lg P, \tag{1}$$

where β is a scale factor, α the power index characterizing distensibility of the vascular bed. In equation (1), when describing the undistended vascular bed, α has the value of 1. Correspondingly, when describing the vascular bed when its resistance to a rise of pressure was increased, $0 < \alpha < 1$, and for vessels whose resistance decreased, $\alpha > 1$. The index β numerically characterizes the scale of the flow characteristics for the blood flow and, consequently, it is the functional equivalent of the geometric size of the vascular bed.

The effect of drugs of the flow characteristics was assessed in each experiment by means of the equation

$$\lg Q=\lg \beta_1+F \lg (\beta_2/\beta_1)+\alpha_1 \lg P+(\alpha_2-\alpha_1)F\lg P, \tag{2}$$

where the index "1" denotes parameters before, and the index "2" those after injection of the drug, the preparation factor F had the value of 0 (for the flow characteristics in the initial state) and 1 (after injection of the drug). Parameters of the flow characteristics before injection (log $\beta_1\alpha_1$), and their changes in response to injection of

Department of Experimental Cardiology, Research Institute of Cardiology, Ministry of Health of the RSFSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 99, No. 6, pp. 708-710, June, 1985. Original article submitted August 17, 1984.

0007-4888/85/9906-0765$09.50

the drug [log (β_2/β_1), $(\alpha_2 - \alpha_1)$] were calculated on the SM-3 computer, using a multiple step regression program. The effect of the drugs on properties of the vascular bed was analyzed statistically by the use of models of the kind:

$$\alpha_2 - \alpha_1 = f(\alpha_1,\ \lg\beta_1),\ \lg\beta_2 - \lg\beta_1 = f(\alpha,\ \lg\beta_1,\ \alpha_2 - \alpha_1), \tag{3}$$

which acquired a concrete form, also with the aid of a multiple step regression program.

EXPERIMENTAL RESULTS

Mean values of α_1 and log β_1 for 25 experiments in the initial state were 1.10 ± 0.05 and 0.32 ± 0.10 respectively. This means that the "statistical mean" vascular bed closely resembles in its properties a linear hydraulic conductor. However, individual values of the parameters varied within a wide range (α_1 from 0.73 to 1.75 and log β_1 from −0.95 to 1.05). This denotes significant qualitative variation of the flow characteristics of the vascular bed in different experiments.

By approximating the distribution of the values of α_1 in different experiments by a lognormal distribution and estimating its parameters, it was possible to determine both the most probable values of α_1 and the 90% confidence interval. Meanwhile, highly significant regression was discovered ($P < 0.001$) between the initial values of α_1 and log β_1: $\log \beta_1 = 2.47 - 1.95\alpha_1$, so that the mean values and 90% confidence interval of log β_1 could be calculated for any values of α_1. The calculated values of α_1 and β_1 are numerical characteristics of the whole range of flow–pressure relations for animals in the initial state (Fig. 1: 1-9). Incidentally, graph 5 corresponds to the most probable initial state of the vascular bed in Fig. 1.

Statistical analysis showed that in the most probable initial state of the vascular bed (Fig. 1: 5) papaverine caused the least and phentolamine the greatest fall of vascular resistance within the range of perfusion pressure examined. The fact will be noted that the greater effect of papaverine was observed with least values of perfusion pressure, whereas for phentolamine and, to some extent, for dihydroergotamine, these relations were opposite. Hence it follows that even when the most probable situation is analyzed, the effect of therapeutic substances is significantly linked with values of blood flow and pressure at which it is estimated. This principle was manifested to an even greater degree with other variants of the flow characteristics for animals in the initial state.

Examination of graphs 1-3, 4-6, and 7-9, reflecting situations with initial ability of the vascular bed to increase its resistance in response to an increase of intravascular pressure ($\alpha_1 < 1$), with little distensibility of the vascular bed ($\alpha_1 \approx 1$), and with a distensible bed ($\alpha_1 > 1$) respectively, clearly shows differences in the effect of the drugs studied. Papaverine, for instance, had the greatest ability to reduce vascular resistance with the lowest initial values of α_1 (see Fig. 1: 1-3; situation with "negative" distensibility). It is considered that the ability of the vessels to increase their resistance in response to an increase of pressure is due to predominance of the myogenic component of arterial vascular tone [6]. Thus papaverine, a vasodilator of myotropic action, had the greatest effect on vascular resistance with initially high myogenic tone. Meanwhile phentolamine had the greatest action on vessels with initially high distensibility (Fig. 1: 7-9).

The most difficult problem is to examine the effect of dihydroergotamine on vascular resistance, for this drug has both a myotropic vasoconstrictor action and a vasodilator α-adrenoblocking action. As will be clear from Fig. 1: 1, 2, in the presence of the smallest "negative" distensibility of the vascular bed and with high values of perfusion pressure, dihydroergotamine caused a decrease in the vascular resistance, but at the same time increased vascular resistance when the intravascular pressure was relatively low. Conversely, with high initial distensibility of the vascular bed (Fig. 1: 8, 9) dihydroergotamine reduced vascular resistance at low values and increased it at high values of pressure. Thus the differences in the effect of dihydroergotamine were attributable to differences in the original variants of distensibility of the vascular bed.

The possibility that the flow characteristics may cross in the real range of values of intravascular pressure is evidence that the perfusion conditions with constant blood flow do not provide reliable information of the principles governing changes in vascular tone under the influence of drugs. It can be concluded from the results that the contradictory information on the trend of the vascular effects of the drugs is based on failure to pay sufficient heed to the conditions of recording vascular resistance and differences in the properties of the vascular bed in the initial state. Meanwhile, analysis of the results, generalized with the aid of an imitation statistical model, not only enables the vascular effects of the drugs to be predicted, but also provides an approach to the elucidation of mechanisms lying at the basis of the variability of their action.

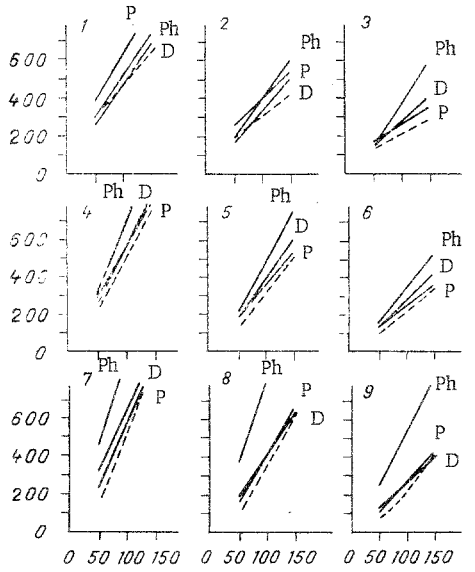

Fig. 1. Effect of vasodilator drugs on flow characteristics of vessels of systemic circulation. Abscissa, perfusion pressure (in mm Hg); ordinate, volume velocity of blood flow (in ml/min). Broken line – regions of flow characteristics before injection, continuous line – after injection of papaverine (P) in a dose of 2 mg/kg, phentolamine (Ph) in a dose of 1 mg/kg, and dihydroergotamine (D) in a dose of 0.5 mg/kg). The effect of the drugs, depending on the initial type of flow characteristics, is described by equations:

$P - \Delta\alpha = -0.193 + 0.206 \log \beta_1$, $\Delta(\log \beta) = 1.136 - 0.092\alpha_1^2 - \Delta\alpha(2.791\alpha_1 - 0.778\alpha_1^2)$;

$Ph - \Delta\alpha = 1.301 - 1.117\alpha_1$, $\Delta(\log \beta) = 0.161 - 0.154 \log \beta_1^2 - (1.700\alpha_1 + 0.506 \log \beta_1^2)\Delta\alpha$;

$D - \Delta\alpha = 0.408 - 0.369\alpha_2^1$; $\Delta(\log \beta) = 0.150 - 0.180\alpha_1 \log \beta_1 - \Delta\alpha(1.274\alpha_1 + 0.853 \log \beta_1)$;

where $\Delta\alpha = \alpha_2 - \alpha_1$, $\Delta(\log \beta) = \log \beta_2 - \log \beta_1$.

Graphs 1-9 plotted for different combinations of parameters α_1 and β_1 in the initial state: 1-3) $\alpha_1 = 0.75$, (1) $\log \beta_1 = 15.5$, (2) $\log \beta_1 = 10.2$, (3) $\log \beta_1 = 6.76$; 4-6) $\alpha_1 = 1.05$, (4) $\log \beta_1 = 3.98$, (5) $\log \beta_1 = 2.63$, (6) $\log \beta_1 = 1.74$; 7-9) $\alpha_1 = 1.50$, (7) $\log \beta_1 = 0.53$, (8) $\log \beta_1 = 0.35$, (9) $\log \beta_1 = 0.23$.

LITERATURE CITED

1. V. A. Almazov, L. P. Larikova, N. K. Merkulova, et al., Kardiologiya, No. 7, 49 (1980).
2. V. V. Buyanov, Farmakol. Toksikol., No. 6, 674 (1974).
3. A. F. Val'dman, V. A. Almazov, and V. A. Tsyrlin, Clinical Neuropharmacology of Hypotensive Drugs [in Russian], Moscow (1978).
4. L. I. Osadchii, Work of the Heart and Vascular Tone [in Russian], Leningrad (1975).
5. A. V. Syrenskii, Krovoobrashchenie, No. 4, 51 (1983).
6. B. Folkow and E. Neil, The Circulation, Oxford Univ. Press (1971).
7. V. M. Khayutin, Fiziol. Zh. SSSR, 44, 645 (1958).
8. V. A. Tsyrlin, B. G. Bershchadskii, L. P. Larikova, et al., Farmakol. Toksikol., No. 1, 71 (1981).