REVIEWS

Object of Regulation in Systemic Hemodynamics

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Systemic hemodynamics characterizing blood circulation, body state, and parameters of correction attracts the attention of scientists and physicians.

The term "regulation" is generally accepted in biology and physiology, it corresponds to terms "operation" and "control" used in technical literature. Automatic control implies stability of a certain parameter or its changes that obey a specified law (program control) or correspond to an external process (follow-up control) affecting regulatory elements of the object. Automatic operation maintains or improves the functioning of some controlled object according to certain requirements.

Systemic hemodynamics is responsible for adequate blood circulation in organs and tissues. A considerable body of data shows nervous, humoral, hemodynamic, and local mechanisms of regulation of systemic hemodynamics. However, there is no consensus on the object of regulation. There are good reasons to believe that blood pressure (BP), cardiac output (CO), or capillary blood flow is the object of regulation. However, it is necessary to emphasize that BP is an integral parameter depending on CO and total peripheral vascular resistance (TPVR). Therefore, BP is maintained at constant level, while CO and TPVR can vary. Since CO only little changes during short-term and long-term BP fluctuations, BP is primarily determined by TPVR. Hence, TPVR is the regulated parameter (by analogy with organ circulation when the blood supply is determined by the diameter of arterioles). If it is granted that BP is the parameter of control, there appears that vascular tone is regulated because smooth muscles change the diameter of vessels under the effects of nervous and humoral factors. The myocardium also possesses these physiological properties; however, the absence of considerable CO variations during nervous and humoral changes in the cardiovascular system suggests that this parameter is not the object of regulation. Some authors report that CO increases to maintain BP during vasodilatation. However, medical practice shows that changes in vascular resistance play the major role during BP fluctuations, especially in cardiovascular diseases, when BP can be normalized with drugs affecting vascular smooth muscles.

Special attention must be given to methods and time of CO measurements during systemic changes. There is no doubt that changes in this parameter should be recorded in the ascending aorta with electromagnetic and ultrasound detectors in the dynamics of the process. However, such measurements are performed only in special studies. Indirect methods (dilution of the indicator and tetrapolar rheography) routinely used in experimental studies and clinics are characterized by low accuracy and do not show whether BP is determined by CO, or CO reflects total changes in this parameter. Therefore, the role of CO in short-term and long-term BP changes remains unclear, and the possibility that CO is the object of regulation in systemic hemodynamics cannot be excluded.

There is a good probability that capillary blood flow is the object of regulation, because oxygen supply to organs and tissues is one of the main functions of the cardiovascular system. It should be noted (as in the case of BP) that capillary pressure is determined by pre- and postcapillary resistances, which depend on

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smooth muscle tone in arterioles and veins. Thus, the target of such regulation can be vascular smooth muscles. Volume blood flow in capillaries depends on the number of functioning capillaries, the state of precapillary sphincters, and blood pressure in arterioles. Therefore, this parameter also cannot be considered as the object of regulation in systemic hemodynamics.

The most important element of regulation in the cardiovascular system is stabilization of systemic BP and minute volume of circulation. In cases of BP changes or systemic transient processes, the question about the object of regulation remains unanswered.

In this report, **systemic hemodynamics** is considered as the interrelation between various parameters responsible for blood circulation in the system.

Experiments of J. Poiseuille (1842) showed that vascular resistance calculated from the simple Poiseuille formula is the difference between BP and venous pressure divided by minute volume of circulation. Since venous pressure is far below BP, it is usually disregarded, and the length of vessels and blood viscosity (practically constant parameters) are not taken into consideration. There is a limitation on extrapolation of Poiseuille' water flow in a cylindrical tube to blood flow in vessels. However, this formula is widely used in clinical and experimental studies and characterizes various processes in the cardiovascular system accompanying changes in systemic circulation. Therefore, the majority of authors assume that the term systemic hemodynamics combines BP, CO, and TPVR. Some limitations and possible errors in CO measurements, as well as the fact that TPVR is the ratio of BP to CO explain ambiguous interpretations of changes in these parameters of systemic hemodynamics.

It should be noted that blood volumes in various regions of the cardiovascular system are different: high-pressure region (left ventricle—arterioles), capillaries, and low-pressure region contain 15-17%, 5-7%, and 75-80% of the total blood volume, respectively. Hence, BP, CO, and TPVR calculated by the Poiseuille formula characterize primarily the arterial bed, but not other compartments of systemic hemodynamics.

Systemic BP, CO, TPVR, heart rate (HR), venous return (VR), central venous pressure (CVP), circulating blood volume, and cardiac work are **the parameters of systemic hemodynamics**.

TPVR determined by direct methods (registration of changes in perfusion pressure under constant blood flow using special devices) not necessary parallels BP in the dynamics of pressure changes. Experiments on narcotized cats showed that the rise in BP in response to vasoactive substances or during pressure reflexes coincides with similar TPVR changes at the beginning of this reaction. TPVR reaches the maximum and then decreases to the initial level, while BP remains at the same level and only later returns to the initial level (Fig. 1).

Thus, changes in BP and TPVR are similarly directed but differ in the time of appearance in the dynamics of systemic reactions, in particular, pressor responses. Moreover, TPVR undergoes only transient changes.

Such interrelations between these parameters result from the facts that, first, the resultant TPVR changes are not the sum of vascular resistances in functionally different organs and tissues, but reflects either opposite changes in resistances in various regions or their different time course, and second, different factors maintain high BP at various periods.

A special methodical complex was elaborated by us to answer these questions and to elucidate the interrelation between the main parameters of systemic hemodynamics during BP changes. Measurements of arterial, venous, and intracardiac pressures, volume blood flow rate, and parameters calculated from these indexes allows us to determine changes in BP, CO, TPVR, HR, blood flows and vascular resistances in the brachiocephalic artery and thoracic aorta beds, blood flows via the anterior and posterior vena cava, total VR, CVP, and cardiac work. This methodical complex allows us to carry out a "controlled experi-

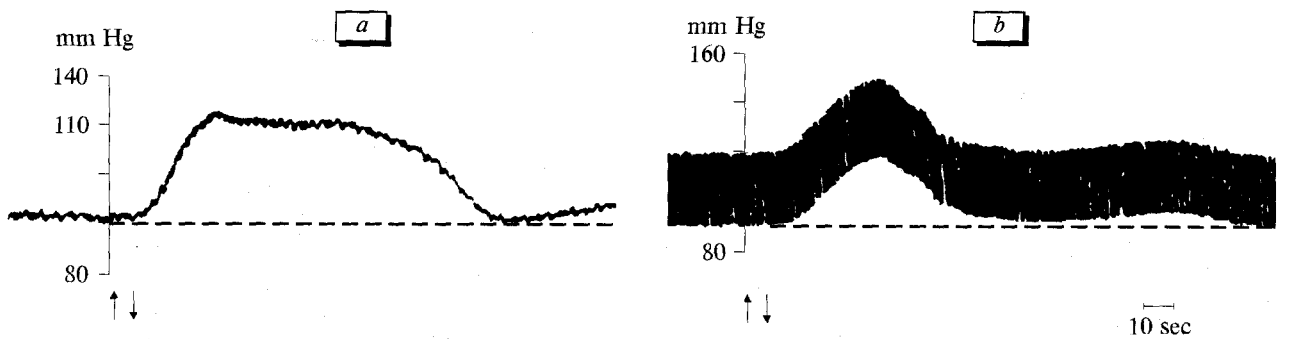

Fig. 1. Changes in systemic blood pressure (*a*) and total vascular resistance in the abdominal aorta bed (*b*) during ileal chemoreflex. Here and in Fig. 2: arrows, the start and end of stimulation.

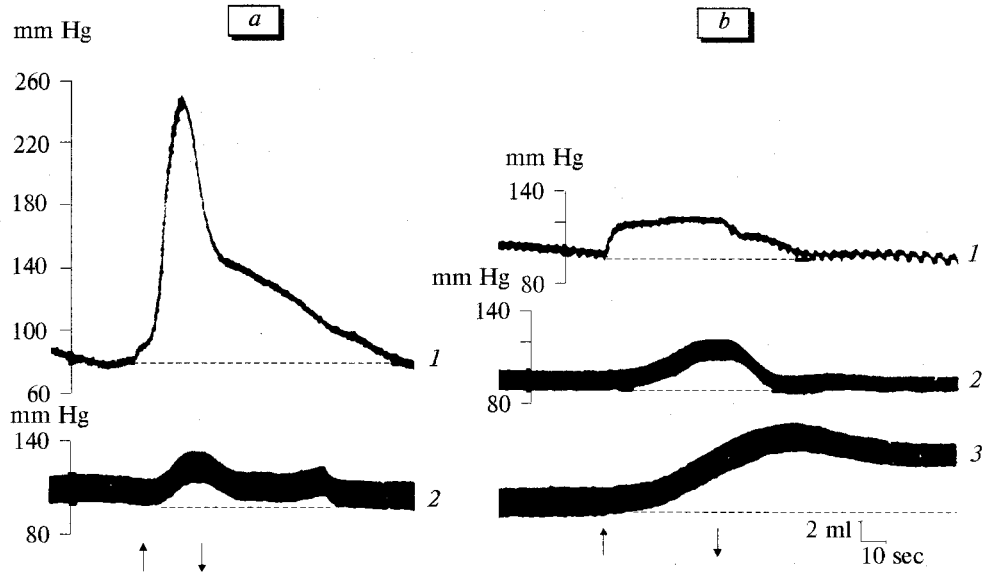

Fig. 2. Interrelation between total blood pressure and vascular resistance in the abdominal aorta bed under conditions of natural (*a*) and stabilized (*b*) blood flow via the posterior vena cava into the right atrium during pressor carotid sinus reflex: *1*) systemic blood pressure, *2*) perfusion pressure in vessels of the abdominal aorta bed, and *3*) blood outflow via the posterior vena cava (the initial value 49.5 ml/min).

ment" on the blood circulation system, i.e. stabilize a certain hemodynamic parameter (CO or VR) at the initial level and determine the type and intensity of changes in remaining parameters. Thus, we can evaluate the role of fixed parameter in systemic hemodynamics. The operating system prevents the increase in blood flow volume during pressor reactions and keeps it unchanged (by automatically controlled pumps) or, by contrast, increases blood volume during depressor reactions, thus maintaining constant blood flow.

During pressor response of the system induced by carotid sinus reflex, the level and the time of BP rise at fixed VR sharply decreased (despite TPVR increase) indicating an important role of VR in this reaction (Fig. 2). These results demonstrate the interrelation between BP and TPVR: the increase in VR and CO contributes to the maintenance of BP at a high level after normalization of TPVR (Fig. 1). In all experiments, the rise in BP is accompanied by the increase in VR, while the remaining parameters increased in 60% observations (Table 1). Therefore, the venous system can supply arterial vessels with the blood. This is quite justified because the venous system contains only 15-17% of the circulating blood.

Thus, it was interesting to study the interrelation between VR and CO during changes in systemic hemodynamics. Controlled experiments showed that pressor response of the system elevated VR, while CO initially decreases and then increases during the same period. When VR was stabilized and did not increase during the pressor response, CO underwent opposite changes within a 2-fold shorter period.

During transient processes in systemic hemodynamics, CO can increase or decrease, while VR generally increases. Taking into account the data on depository functions of pulmonary vessels, we assume that the interrelation between CO and changes in the pulmonary circulation hemodynamics can underlay such variability of CO changes. In this case, CO is lower than VR because the blood entering the right heart via

TABLE 1. Effects of Catecholamines on Parameters of Systemic Hemodynamics (% of Observations)

Substance	BP	CO	TPVR	VR	HR	SV	LVW	Changes
Epinephrine, 5-10 μg/kg	100%	75	67	92	67	83	92	↑
	—	25	33	8	25	17	8	↓
	—	—	—	—	8	—	—	0
Norepinephrine, 1-2 μg/kg	100%	69	77	100	62	62	85	↑
	—	31	23	—	38	38	15	↓
	—	—	—	—	—	—		0

Note. SV: stroke volume; and LVW: left ventricular work. Here and in Table 2: ↑ and ↓ show increase and decrease in the parameter, respectively; 0: no changes.

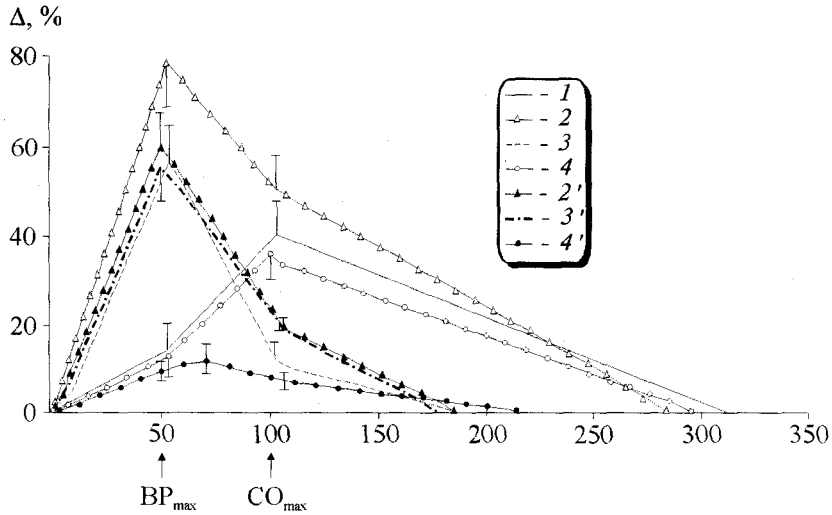

Fig. 3. Changes in blood circulation induced by 10-20 μg/kg epinephrine under conditions of natural changes in cardiac output (*1-4*) and its stabilization (*2'-4'*). Abscissa: time of reaction (sec). Arrows: periods of maximum increase in blood pressure (BP) and cardiac output (CO). *1*) Cardiac output; *2* and *2'*) blood pressures; *3* and *3'*) total peripheral vascular resistances; and *4* and *4'*) venous return.

the vena cava is partially deposited in the pulmonary circulation. At the same time, CO can surpass VR due to blood release from the pulmonary into systemic circulation.

However, it was unclear why CO remains practically constant during changes in the cardiovascular system, while TPVR considerably varies. There are several explanations of this fact. First, judging from the Poiseuille formula, TPVR markedly varies during considerable BP changes at constant CO. Second, changes in CO occurring during any reaction stage are difficult to record because of discreteness of the method of indicator dilution. Third, the low-pressure system have some characteristic mechanisms, which (in the case of appropriate regulation of the interrelation between VR, blood flow in pulmonary circulation vessels, and CO) compensatory reduce blood supply to the arterial system, for example, they prevent the rise in CO against the background of a considerable increase in TPVR. The absence or impairment of these mechanisms in diseases can cause a sharp rise in BP, especially under the effects of vasoactive substances.

Experiments with epinephrine showed that the maximum rise in BP (Δ=80%) at the 50th sec of the reaction was accompanied by the greatest increase in TPVR (Δ≈60%), while VR and CO increased only by 10% (Fig. 3). At the same time, BP remained high (Δ=50%) at the 100th sec of the reaction, when VR and CO reached maximum (Δ=40%), while TPVR increased only by 10%. It should be emphasized that further decrease in BP to the initial level occurred in parallel with the decrease in VR and CO (Fig. 3).

Thus, all these methods (simultaneous measurement of BP and vascular resistance in the thoracic aorta, stabilization of VR, and determination of the time over which BP and CO reach maximum) indicate that initial stages of the pressor response is accompanied by a sharp increase in TPVR and minor changes in VR and CO. Then, vascular resistance decreases, while VR and CO increase. Such interrelation between these parameters of systemic hemodynamics determines the increase and further decrease in systemic BP. Hence, TPVR plays the major role in the catecholamine-induced increase in BP, while VR and CO are responsible for the maintenance of BP at a high level. BP is then normalized due to the decrease in VR and CO.

Catecholamines sharply decreased the degree and duration of VR changes in case of CO stabilization at the initial level in the controlled experiment (Fig. 3). This effect was similar to CO changes observed during VR stabilization (Fig. 2). The mechanisms of CO effects on the venous blood return to the right heart remain unclear, but the presence of strong interrelations is beyond doubt. These mechanisms are responsible for working or reactive hyperemia observed in intensely functioning organs during hypovolemia.

The mechanisms responsible for blood return to the heart and changes in VR in each vena cava are of considerable interest (Table 2). Pressor substances increase BP and TPVR and cause biphasic changes in CO and VR. These effects depend on the degree and time of the blood flow increase in each vena cava. The decrease in BP and TPVR induced by depressor substances was not accompanied by changes in CO and VR due to compensatory changes in blood flow via each vena cava. Blood flow via the anterior vena cava generally increases irrespective of the type of BP and TPVR changes. VR and CO reach the control values or undergo biphasic changes due to blood flow variations in the posterior vena cava (Table 2). However, these results were obtained in experiments on animals exposed to thoracotomy and placed in a horizontal position. Thus, these mechanisms in humans that are in a vertical position and under hydrostatic load require further investigations.

CVP probably regulates blood inflow via the vena cava during opposite and unidirectional changes in blood flow.

Changes in CVP and its effects on various parameters of systemic hemodynamics in response to intravenous injection of norepinephrine were studied (Fig. 4). BP increased due to the rise in TPVR, which reached the maximum and then decreased to the initial level, while BP remained high. At the initial period of this systemic reaction, a sharp rise in CVP induced initial drop of VR and CO due to reduced blood flow via the posterior vena cava and unchanged blood flow via the anterior vena cava. Simultaneous decrease in CVP to the initial level and normalization of TPVR were accompanied by a rise in VR and CO due to enhanced blood flow via the anterior and posterior cava veins (Fig. 4). These changes contributed to the maintenance of BP at a high level; this parameter then gradually decreased with the decrease in VR and CO.

Studies of the interrelation between parameters of systemic hemodynamics during the pressure response showed that transient increase in TPVR underlies these shifts. CO increases due to VR rise via the anterior and posterior cava veins. Final changes in CO are determined by CVP, pulmonary circulation capacity, and hemodynamic status contributing to adequate oxygen supply to functioning organs and tissues.

Thus, BP pressor fluctuations are accompanied by short-term increase in TPVR and readjustment of CO determined by complex interrelations between VR, CVP, and blood volume in pulmonary vessels. A question arises: what is the object of regulation in systemic hemodynamics? Stable reactions of the arterial system and various interrelations between parameters of the low-pressure system should correspond to changes at the organ and microcirculatory levels, which require further investigations.

Under similar conditions (measurements of perfusion pressure at a constant perfusion volume), the increase in vascular resistance in various regions in response to the same stimuli greatly varied (Fig. 5). During vasomotor reflexes in cats, vasoconstriction observed in the peritoneal cavity was less pronounced than vasoconstriction in skeletal muscles but surpassed coronary, cerebral, and pulmonary vasoconstriction.

Vascular reactions in various regions probably depend on sympathetic innervation and the intensity of sympathetic impulses; different content, sensitivity, and distribution of α- and β-adrenoceptors; effects of local factors, especially metabolites; and biophysical peculiarities of the vessels. Passive changes in vessels determined by their dilatation in response to BP fluctuations or caused by extravascular factors can differ from (or add to) active changes. However, this problem is not discussed in this work.

The following question remains unclear: why the sympathetic nervous system increases vascular resistance in all organs during sympathoadrenal effects accompanying many types of body vital activity (physical exercises and intellectual work) or in stress, when vasodilatation is necessary to supply intensely functioning organs with oxygen and nutrients? This vasodilatation do occur due to local mechanisms, contrary to constrictor effects of the sympathetic nervous system (although cholinergic sympathetic fibers were found in mammalian skeletal muscle vessels). In this case, BP should decrease during reactive hyperemia in various organs, vasodilatation, and recruitment of nonfunctioning capillaries under conditions of limited arterial blood volume (15-17%); however, this parameter increases. Therefore, TPVR is not the object of regulation in systemic hemodynamics, and its changes is a protective reaction for blood redistribution (during blood loss, hyper- and hypothermia, digestion, and sexual arousal) into the system playing the major role under conditions of limited blood volume in the arterial system. That is why, the majority of people are unable to perform simultaneously various tasks. In this case, CO should regulate VR to prevent volume overload and the increase right atrial pressure.

Experiments on cats using the method of accumulography (registration of venous blood outflow from the organ to an extracorporeal reservoir under constant volume of the blood delivered through a perfusion pump) demonstrated that blood flow changes in the vena cava are determined by labile capacity of its vessels. Stimulation of the carotid sinus was accompanied

TABLE 2. Changes in Parameters of Systemic Hemodynamics Induced by Pressor and Depressor Agents

Substance	BP	TPVR	HR	CO	VR	PVCBF	AVCBF
Norepinephrine	↑	↑	↓	↑↓	↑↓	↑↓	↑
Angiotensin amide	↑	↑	↓	↑↓	↑↓	↓	↑
Acetylcholine	↓	↓	↑	0	0	↓	↑
Histamine	↓	↓	↑	0	0	↓	↑

Note. ↑↓, biphasic changes. PVCBF and AVCBF, blood flow via the posterior and anterior vena cava, respectively.

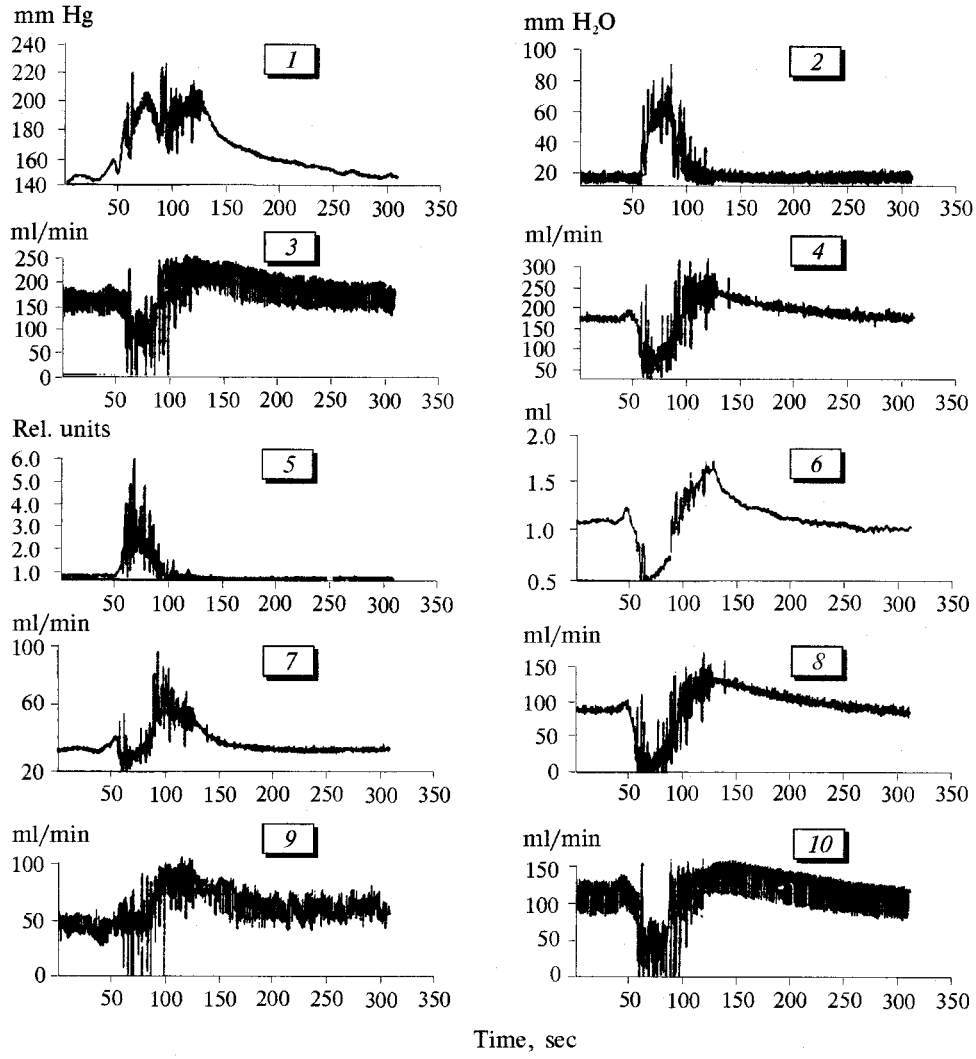

Fig. 4. Parameters of systemic hemodynamics after intravenous injection of 10 μg/kg norepinephrine. Systemic blood pressure (*1*); central venous pressure (*2*); total venous return (*3*); cardiac output (*4*); total peripheral vascular resistance (*5*); stroke volume (*6*); blood flow in the brachiocephalic artery (*7*), thoracic aorta (*8*), and anterior (*9*) and posterior (*10*) vena cava.

by the increase in skeletal muscle vascular resistance, while their vascular capacity decreased, increased, underwent biphasic changes, or remained constant (Fig. 6). Various changes in vascular capacity were observed in the stomach, small intestine, and lungs, while cerebral and coronary vasoconstrictory responses were always accompanied by a decrease in vascular capacity. The maximum decrease in venous vessel capacity always preceded the increase in vascular resistance under stimulation of the corresponding sympathetic nerves. The maximum response in arteries was observed at a lower frequency of sympathetic nerve stimulation than in veins.

Thus, changes in the capacity of organ vessels and electric stimulation of sympathetic nerves confirmed the assumption that organ vessels have labile systems responsible for the maintenance of adequate VR and demonstrated the mechanism of additional blood release to circulation or blood deposition in veins. Experiments with ganglioblockers applied in pharmacological doses showed that they prevent the increase or decrease in vascular resistance but had no effect on vascular capacity. Only a 2-3-fold increase in the dose of ganglioblockers abolished the reflex changes in vascular capacity. These data demonstrate the stability of fine mechanisms responsible for adequate VR at the organ level.

Various changes in the vascular capacity in the majority of organs in response to nervous or humoral stimuli are probably due to active reactions of their veins or filtration-absorption relationships between the vascular and interstitial spaces. This problem was analyzed at the microcirculatory level by measuring the mean capillary hydrostatic pressure (by a gradual decrease in the blood flow through the organ and simultaneous increase in venous outflow pressure to at-

taining an equilibrium between filtration and absorption) and capillary filtration coefficient (by the increase in venous pressure in the vascular bed perfused with constant blood volume followed by the use of the modified Starling formula). Pre- and postcapillary resistances and their ratio that determines the level of capillary pressure were calculated from perfusion, capillary pressure, and venous pressure to reveal the mechanisms responsible for microhemodynamic changes.

We studied changes in microhemodynamics induced by various exogenous stimuli under above described conditions. A comparison of microhemodynamic changes in cerebral vessels induced by ATP and hypoxia against the background of reduced perfusion pressure showed opposite variations in capillary pressure and capillary filtration coefficient (Fig. 7). The ratio between pre- and postcapillary resistances decreased under the effect of ATP and increased in hypoxia (due to the decrease in postcapillary resistance). Under the effect of ATP or hypoxia, capillary pressure underwent opposite changes, which determine filtration of the fluid from capillaries to the interstitial space and its absorption from the interstitial space to capillaries, respectively. These factors caused also opposite changes in the coefficient of capillary filtration, venous pressure, and spinal fluid pressure. Thus, similar shifts in perfusion pressure fluctuations (cerebral vasodilatation) were accompanied by various changes

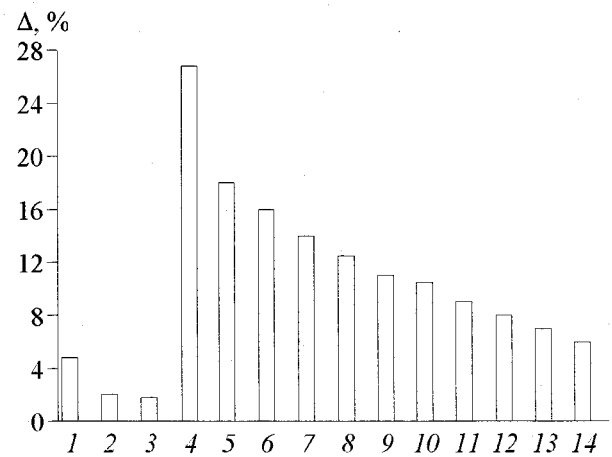

Fig. 5. Changes in vascular resistance (active reaction) in various regions of the circulation system during pressor reflex: vessels of the heart (*1*), brain (*2*), lungs (*3*), pelvis and hindlimbs (*4*), both hindlimbs (*5*), hindlimb (*6*), pelvic muscles (*7*), kidney (*8*), large intestine (*9*), spleen (*10*), forelimb (*11*), stomach (*12*), ileum (*13*), and liver (*14*).

in veins, which altered filtration-absorption interrelations and VR to the heart.

Analogously, coronary vasodilators (obsidan and corinfar) induced changes in microhemodynamic parameters not only in the heart, but also in other organs. Experiments on cats showed that precapillary sphincters of small intestine vessels opened and, therefore, the coefficient of capillary filtration increased under effects of these drugs. At the same time, corinfar in-

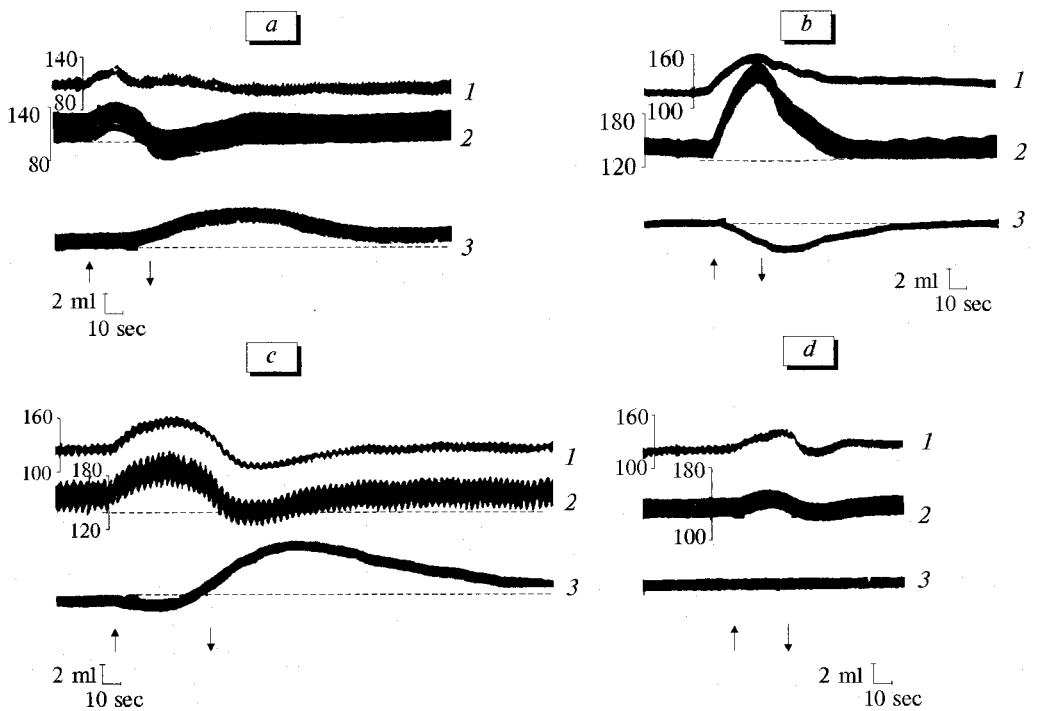

Fig. 6. The decrease (*a*), increase (*b*), biphasic changes (*c*), and no changes (*d*) in vascular capacity against the background of increased muscle vascular resistance during the pressor reflex in cats: blood pressure (mm Hg, *1*), perfusion pressure (mm Hg, *2*), and venous blood outflow (ml, *3*). Arrows: start and end of stimulation.

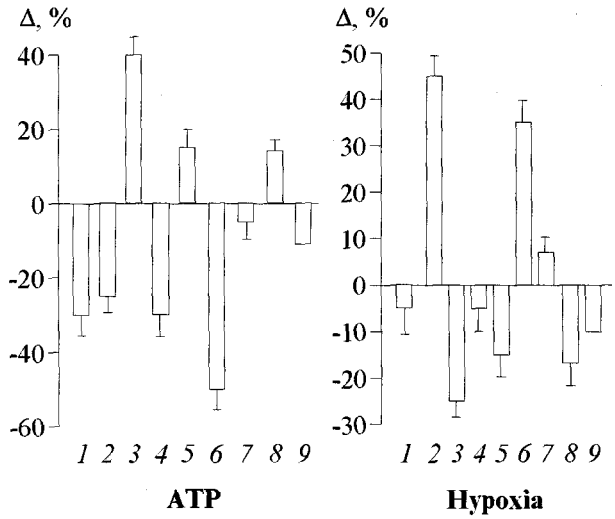

Fig. 7. Changes in macro- and microhemodynamics in cat cerebral vessels 5 min after intracarotid infusion of ATP (0.3 mg/min) and during 5-min hypoxic hypoxia (8% O_2 in nitrogen). *1*) Perfusion pressure, *2*) capillary filtration coefficient, *3*) capillary hydrostatic pressure, *4*) pre- and *5*) postcapillary resistances, *6*) ratio between pre- and postcapillary resistances, *7*) spinal fluid pressure, *8*) venous pressure, and *9*) venous outflow.

creased capillary pressure, while obsidan decreased this parameter. This indicated the ambiguity of changes in filtration-absorption interrelations at the microcirculation level under conditions of increased blood supply to the organ.

These findings indicate that even narcotized animals placed in a horizontal position have fine mechanisms responsible for changes in the vascular capacity at the organ and microcirculatory levels determined by changes in venous tone and filtration-absorption interrelations in capillaries. These mechanisms are responsible for adequate blood supply to the cava veins in accordance to the hemodynamic status and systemic goal. Vertical position and hydrostatic load in humans obviously imply the presence of additional mechanisms in the low-pressure systems (in particular, muscle pump and pumping strength of the thorax and right atrium).

What is the object of regulation in systemic hemodynamics and at what level this parameter is regulated, if blood flow in the vena cava, VR, changes in vascular capacity, venous tone, and variations in capillary filtration-absorption interrelations depend on its changes? The data presented here indicate that BP and TPVR are not the objects of regulation. Such regulation of the parameter (or changes in this parameter) that controls 70% of blood volume in the low-pressure system or blood redistribution into arterial vessels of the active physiological system is performed at the level of CVP-pulmonary blood volume. It remains to be studied, which of these parameters plays the major role in the regulation of changes in systemic hemodynamics.