# GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

# Differences in Brain and Liver Blood Flow During and After Acute Blood Loss in Rats with Different Resistance to Circulatory Hypoxia

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Variations of blood flow and vascular resistance in the common carotid arteries and of blood flow in the hepatic artery and portal vein are examined during and after acute massive blood loss in rats with low and high resistance to circulatory hypoxia. In rats with low resistance, arterial pressure and the rates of cerebral and hepatic blood macro- and microflow, which have decreased during blood loss, continued to fall during the posthemorrhagic period. After cessation of bleeding, a transient arterial pressure rise to 70 mm Hg is observed in rats with high resistance, while the blood flow via carotid arteries increases to 65% of its initial value, being maintained at this level throughout the period of changes in carotid vascular resistance; intrinsic hepatic arterial blood flow increases to 115% of baseline value, while the portal vein blood flow and hepatic microflow increase to 75%.

**Key Words:** *blood loss; brain; liver; blood flow; ultrasound, laser*

The evidence in favor of individual sensitivity to hypoxia has been accumulated. Biochemical studies show that some parameters of lipid, carbohydrate, and energy metabolisms as well as the phospholipid composition of plasma membranes are different in animals with different sensitivity to hypoxia [1,2,10, 11]. Metabolic processes strongly depend on tissues blood flow and microcirculation [14]. However, individual sensitivity of cardiovascular system to hypoxia has not been studied in sufficient detail.

Previously, we reported that rats with different sensitivity to circulatory hypoxia develop two types of systemic arterial pressure (AP) and portal macro- and microcirculation responses to acute blood loss [6]. Transient compensation of AP and hepatic blood macro- and microflow was observed in rats with high resistance to blood loss (HR rats) during the posthemorrhagic period. These rats survived for at least 3 h after the cessation of bleeding. In rats with low resistance to circulation hypoxia (LR rats), no posthemorrhagic restoration of AP or hepatic blood flow was observed, their hepatic and intestinal microvasculatures remained constricted, and these rats died during the first hour cessation of bleeding. The pathogenesis of these hemodynamic changes is linked to impaired neuropeptide regulation of AP and portal circulation and to hyperactivation of central muscarine receptors in the brain [5].

In the present study we examined cerebral blood flow and hepatic macro- and microcirculation in rats with compensated or primarily decompensated AP response after massive blood loss. The state of cerebral circulation was assessed by recording temporal variations of blood flow through the common carotid

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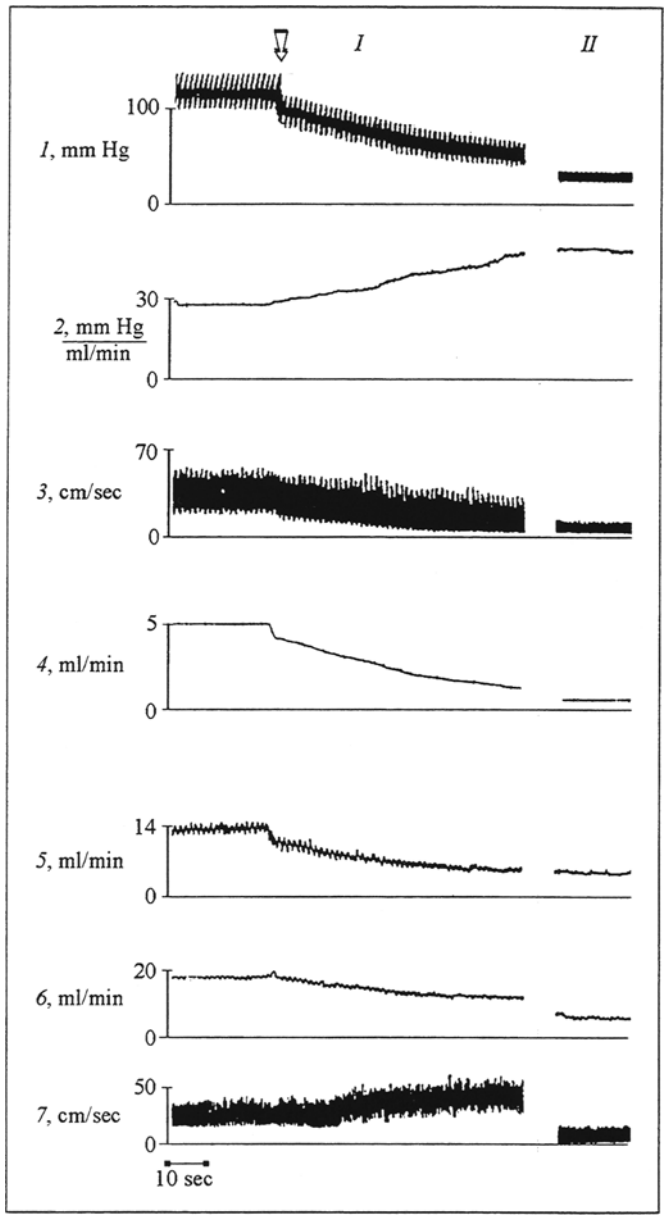


**Fig. 1.** Variations of the major hemodynamic parameters of macro- and microcirculation in rats during rapid reduction in the volume of circulating blood. The beginning (*I*) and the end (*II*) of bleeding. *1*) pulse pressure; *2*) vascular resistance in the left common carotid artery; *3*) linear blood flow rate in the left carotid artery; *4*) volume blood flow rate in the left carotid artery; *5*) blood flow in the portal vein; *6*) hepatic blood microflow (per 100 g liver weight); *7*) blood flow rate in the hepatic artery. The arrowhead marks the start of bleeding.

arteries, which adequately reflects the extent of brain perfusion [9,13].

## MATERIALS AND METHODS

Experiments were performed on 42 male Wistar rats (200-250 g) under urethane anesthesia (1.25 g/kg intraperitoneally). Hemodynamics was evaluated using an ultrasonic Doppler apparatus developed at the Bioengineering Laboratory, Institute of General Pathology and Pathophysiology, Moscow. The apparatus allowed a simultaneous record of blood flow in various vascular beds [7]. Arterial pressure was measured in the right femoral artery with a micromanometer; linear and volume blood flow rates in the left common carotid artery were measured using a bandage ultrasonic sensor (1 mm) calibrated in units of volume blood flow and operating at a frequency of 27 MHz. The real time vascular resistance in the left common carotid artery was determined with a built-in computer. In some rats, blood flow rates were simultaneously measured in the left and right common carotid artery. The intrinsic portal blood flow was measured with the use of a bandage-type ultrasonic sensor connected to a special unit providing electronic separation of the arterial blood flow curve from the total signal [4,8]. The hepatic blood microflow was recorded with an ALF-21 laser Doppler flowmeter (Advance Co., Ltd.). Acute blood loss was produced by a single 5-min bloodletting from the left femoral artery in the amount equal to 2.5% of body weight. The observation time after the beginning of bleeding was 2 h. The data were analyzed by Fisher—Student test.

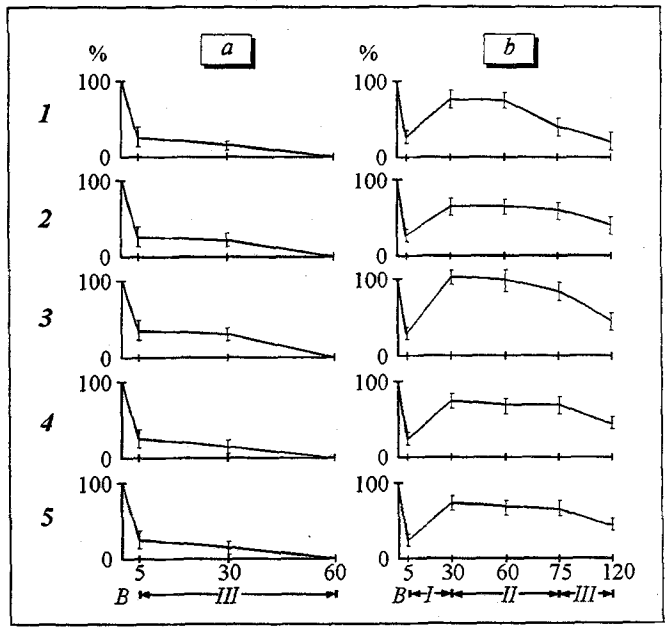


**Fig. 2.** Variations of arterial pressure and cerebral and hepatic blood flows in different phases of acute blood loss in rats with low (*a*) and high (*b*) resistance to hypoxia. *B*) blood loss; *I*) recovery phase; *II*) phase of relative stabilization; *III*) terminal phase. *1*) arterial pressure; *2*) blood flow in the left common carotid artery; *3*) blood flow in the hepatic artery; *4*) blood flow in the portal vein; *5*) hepatic blood microflow. Abscissas: time after bleeding was stopped, min; ordinates: parameter values (in % of baseline taken as 0).

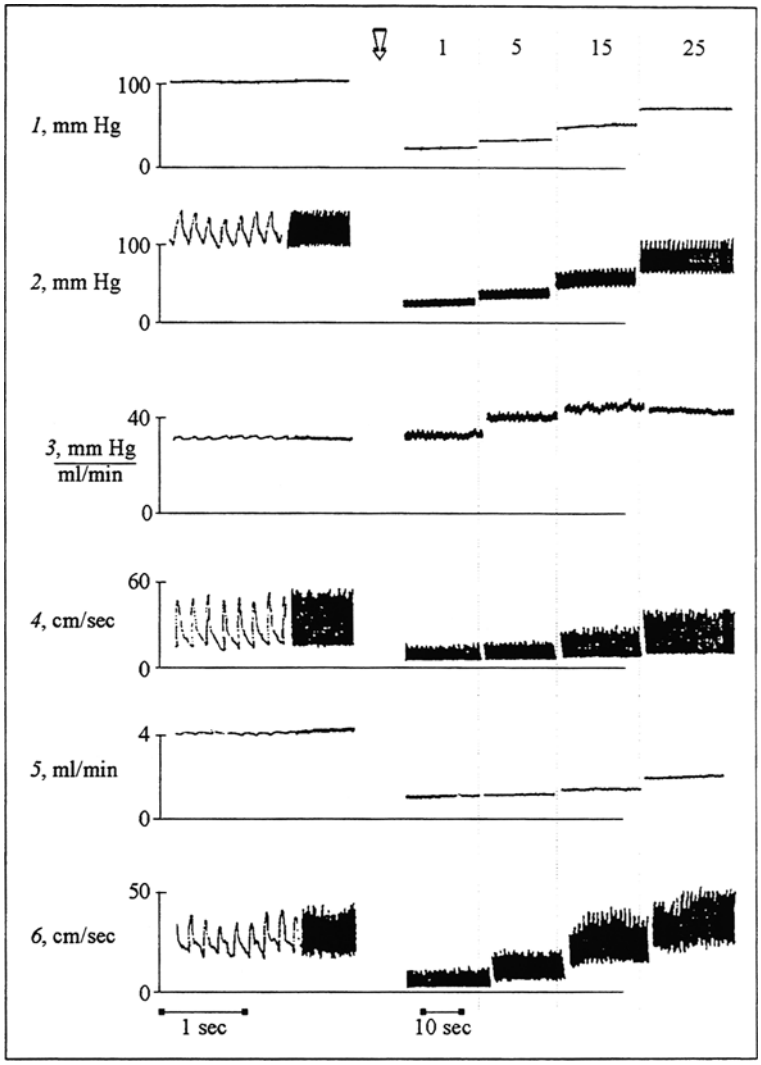


**Fig. 3.** Temporal variations of arterial pressure (AP) and carotid and hepatic arterial blood flows in high resistant rats after cessation of acute massive bleeding. The arrowhead indicates the beginning of posthemorrhagic period; figures on top are minutes after cessation of bleeding. *1*) mean AP; *2*) pulse pressure; *3*) vascular resistance in the left common carotid artery; *4*) linear blood flow rate in the left carotid artery; *5*) volume blood flow rate in the left carotid artery; *6*) blood flow in the hepatic artery.

## RESULTS

No statistically significant differences were found in the of blood flows between the left and right common carotid arteries in intact rats (before bleeding) and in the variations of these flows with time during and after bleeding. All rats, regardless of their individual susceptibility to circulatory hypoxia, showed a rapid fall in AP and in linear and volume blood flow rates in the common carotid arteries immediately after beginning of bleeding (Fig. 1). Carotid resistance remained unchanged in some rats and rose or fell in others. The volume rate of intrinsic portal blood flow decreased, whereas the rate of hepatic arterial blood flow increased. Alterations of the hepatic blood microflow measured by the laser Doppler flowmeter usually correlated with those of blood flow in the portal vein measured by the ultrasonic sensor. The loss of about 50% of the circulating blood reduced AP to a level below 30 mm Hg in all rats regardless of their individual sensitivity to blood loss. The amount of blood entering the liver via the portal vein and hepatic artery and the brain via the common carotid arteries dropped to 20-25% of that before blood loss. The resistance of the common carotid arteries increased in most LR rats and, as a rule, remained above baseline until they died. In these rats, the rates of cerebral blood flow and hepatic intrinsic and tissue blood flows, which had reduced during bleeding, continued to fall slowly during the posthemorrhagic period, and the animals died 1 h after the bleeding was stopped (Fig. 2).

In HR rats with compensated posthemorrhagic period, AP progressively rose after cessation of bleeding (Fig. 3), being 72±12% of baseline by the 30th min; blood flow in the common carotid arteries were restored to 63±13.5% of baseline and (in the presence of spontaneous posthemorrhagic fluctuations of AP) was maintained at that level due to changes in carotid resistance. The liver blood flow was also

restored temporarily but, in contrast to the cerebral blood flow which failed to be restored, the self-compensation of hepatic intrinsic arterial blood flow amounted to 115±15% of baseline value. An increase in the intrinsic portal blood flow and hepatic blood microflow did not exceed 75% (Fig. 2). In the HR group, the irreversible decline of AP in the terminal phase of the posthemorrhagic period began earlier compared with a decrease in hepatic and cerebral blood flow. The relative stability of cerebral blood flow was due to diminished carotid resistance.

Thus, autoregulation of cerebral blood flow was overwhelmed in both LR and HR rats during bleeding due to rapid fall in AP, which agrees with the observations of others [10]. Linear and volume blood flow rates in the common carotid arteries progressively decreased to 20-25% of baseline values by the end of bleeding.

Unlike the carotid arterial blood flow, hepatic arterial blood flow was relatively independent of AP. An autoregulatory increase in the arterial fraction of the total hepatic blood flow was recorded at the beginning of bleeding. Hepatic blood microflow, as measured with the laser Doppler flowmeter, also decreased in most cases, which may be due to the fact that flowmetry measures blood flow predominantly in superficial hepatic microvessels (portal and hepatic venules and sinusoids). Since hepatic arterioles lie deeper in the organ [3], the possibility of measuring blood microflows rates in them is limited.

After cessation of bleeding, cerebral and hepatic blood flows in LR rats remained at very low levels, and these animals failed to develop centralization of circulation whereby blood is redistributed to the internal organs most sensitive to hypoxia. In our experiments, circulation was centralized only in HR rats in which the posthemorrhagic period included a phase of temporary self-compensation of the AP, cerebral blood flow, and hepatic macro- and microcirculation. Posthemorrhagic stabilization of the amount of blood entering the brain via the common carotid arteries at a level not exceeding 65% of the baseline value was actively regulated through changes in the carotid vascular resistance. Posthemorrhagic increase in arterial blood flow to the liver was nearly 2 times greater than that in the carotid arterial blood flow. The preferential blood supply to the liver in HR animals may be associated with the following functions of the liver. It is the major organ supplying glucose to the blood, and 70% of glucose produced by the liver is consumed by the brain [10]. Disturbances in protein synthesis and metabolic and phagocytic functions of the liver in shock and acute blood loss are the main factors in the development of progressive multiorgan insufficiency incompatible with life [12-14]. Therefore, an adequate restitution of intrinsic hepatic blood flow and microcirculation is necessary for liver functioning at a subnormal level, which will allow the brain and other organs to provide functional integrity of the organism under the adverse conditions following massive blood loss.

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