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# PARAMETERS OF THE SYSTEMIC HEMODYNAMICS IN CONSCIOUS RATS WITH ACUTE STREPTOZOTOCIN DIABETES

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**KEY WORDS:** experimental diabetes mellitus; hemodynamics; vasodilatation

Disturbances of functions of the cardiovascular system are frequently observed in patients with diabetes mellitus. Among the important causes of these disturbances are multiple microangiopathies [7]. It is considered that microvascular lesions in diabetes may have a hemodynamic basis [9, 15], and they may arise as a result of vasodilatation in the initial stages of the disease, followed by elevation of the capillary pressure and increased blood flow [14, 15]. An increased blood flow has been found in many tissues during short-term insulin-dependent diabetes [6, 7, 10]. Functional microvascular changes may arise at the end of the prediabetic phase and may be preceded by degenerative changes in the vessels [3]. It has been suggested that in order to play a primary, key role, vasodilatation must be recorded on the 1st day of diabetes [12, 13].

This paper describes a study of changes in the basic parameters of the systemic hemodynamics – arterial blood pressure (BP), cardiac index (CI), calculated as the cardiac ejection per 100 g body weight, and the total peripheral vascular resistance (TPVR) – in conscious rats with acute streptozotocin-induced diabetes (24 h after injection of streptozotocin).

## EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 350-450 g. The cardiac output was determined by the thermodilution method, using a "Cardiomax" instrument (USA). Through a catheter implanted beforehand in the jugular vein, 0.2 ml of cold physiological saline was injected into the animal. By means of a thermocouple implanted in the aorta, the thermodilution curve was recorded, and on that basis cardiac output was calculated. BP was recorded by means of a "Statham 23D" pressure transducer through a catheter implanted in the abdominal aorta through the femoral artery. The parameters were recorded on a "Nihon Kohden" polygraph (Japan). On the basis of the values obtained for cardiac output, heart rate (HR), and BP, values of CI, the stroke blood volume (SV), and TPVR were calculated. Parameters of the systemic hemodynamics were measured in conscious animals 2 days after the operation. For this purpose, the thermodilution curve and BP were recorded three times at intervals of 5 min. The values of BP, CI, TPVR, HR, and SV thus obtained were averaged. Next, diabetes was induced in the animal by a single injection of streptozotocin (STZ) (from "Upjohn," USA) in a dose of 50 mg/kg through a venous catheter (the solvent was citrate buffer, pH 4.5). The glucose and ketone

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TABLE 1. Parameters of Systemic Hemodynamics before and 1 Day after Injection of Streptozotocin in Rats with Intact Sympathetic Nervous System and Desympathized Rats

| Parameter of systemic hydrodynamics | Intact rats, n = 7 | | Desympathized, n = 6 | |
|---|---|---|---|---|
| | before injection of STZ | 1 day after injection of STZ | before injection of STZ | 1 day after injection of STZ |
| Blood pressure, mm Hg | 114,6±6,5 | 101,9±4,9* | 102,7±2,1 | 92,8±3,5* |
| Cardiac index, ml/min × 100 g | 35,6±1,50 | 43,9±2,80* | 45,1±3,60+ | 46,4±2,54 |
| Total peripheral vascular resistance, mm Hg/ml/min × 100 g | 3,25±0,22 | 2,38±0,20** | 2,35±0,20+ | 2,00±0,12* |
| Heart rate, beats/min | 398±21,0 | 383±18,0 | 405±5,0 | 395±8,0 |
| Stroke volume, ml | 0,43±0,033 | 0,54±0,045** | 0,39±0,029 | 0,42±0,022 |

**Legend.** *$p < 0.05$; **$p < 0.01$ compared with value before injection of STZ (paired t test); +$p < 0.05$ compared with IR (unpaired t test).

levels in the urine were measured 1 day after injection of STZ in the rats by means of "Multistix" reagent strips ("Ames," Great Britain). If glucose was present in the urine, the parameters of the animal's systemic hemodynamics were again measured. At the end of the experiment the blood glucose level was measured by means of a glucometer ("Miles," USA). Animals whose blood glucose level exceeded 350 mg% were considered to be diabetic. To determine the role of the sympathetic nervous system in the development of changes in the parameters of the systemic hemodynamics in rats with acute diabetes, diabetes was induced in another series of experiments in chemically desympathized rats. Desympathization was caused by two injections of 6-hydroxydopamine in a dose of 50 mg/kg intravenously, at an interval of 24 h. Under superficial ether anesthesia, 4 days after the first injection of 6-hydroxydopamine, catheters and a thermocouple were implanted in the animal, which was used in the experiments 2 days later. The results were subjected to statistical analysis by Student's paired and unpaired t tests and are given below in the form M ± m.

## EXPERIMENTAL RESULTS

The glucose levels of all the animals 1 day after injection of STZ were considerably raised: more than 55 mM in the urine and 21.0 ± 1.5 mM in the blood (378 ± 27 mg%). No ketones were found in the urine.

Parameters of the systemic hemodynamics before and 24 h after injection of STZ in rats with an intact sympathetic nervous system (IR) and in desympathized rats (DR) are given in Table 1.

In IR 1 day after injection of STZ lowering of BP by 11% ($p < 0.05$), an increase in CI by 12% ($p < 0.05$), reduction of TPVR by 27% ($p < 0.01$), and an increase in SV by 26% ($p < 0.01$) were observed. There was no significant change in HR.

Compared with IR, DR were characterized by a significant decrease in TPVR (by 28%, $p < 0.05$) and an increase in CI (by 27%, $p < 0.05$). There was no significant change in BP and HR. SV, calculated per 100 g body weight, was somewhat higher in DR than in IR.

In DC 1 day after injection of STZ BP was 10% lower ($p < 0.05$) and TPVR 15% lower ($p < 0.05$). There was no significant change in CI, SV, or HR.

Changes in parameters of the systemic hemodynamics in IR and DR 1 day after injection of STZ compared with preinjection values are shown in Fig. 1.

Thus a significant change in parameters of the systemic hemodynamics was observed in IR 1 day after injection of STZ (Fig. 1). BP fell but CI rose significantly, and TPVR was reduced. CI rose as a result of an increase in SV. DR were characterized by a significantly lowered TPVR accompanied by a raised CI, in agreement with previous findings [1, 2], and serves as an indirect indicator of the efficacy of desympathization. Lowering of BP and TPVR was observed in DR 1 day after injection of STZ. There was no change in CI, SV, or HR (Fig. 1).

It can be concluded from the results that 1 day after injection of STZ a significant change in parameters of the systemic hemodynamics can be observed in both IR and DR, and that in both cases BP falls as a result of systemic vasodilatation. It is important to note that with the same percentage relative fall of BP, the structure of the response in IR and DR differed completely (Fig. 1). In the first case there was a significant increase in CI and SV, whereas in the second case these

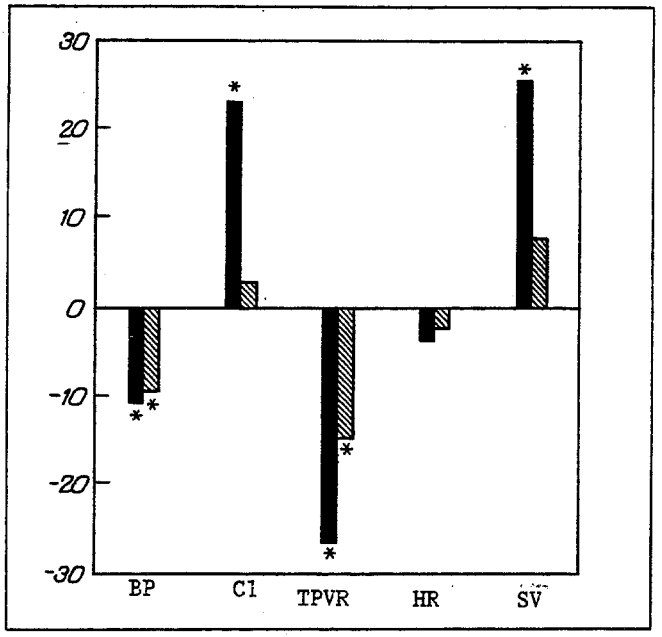


Fig. 1. Changes in parameters of systemic hemodynamics in intact and desympathized animals 1 day after injection of streptozotocin compared with preinjection level. Abscissa, parameters of systemic hemodynamics studied; ordinate, changes in parameters (in per cent compared with value before injection of streptozotocin. BP) Blood pressure, CI) cardiac index, TPVR) total peripheral vascular resistance, HR) heart rate, SV) stroke volume of the heart. *$p < 0.05$ compared with level before injection of streptozotocin. Black columns indicate intact rats, obliquely shaded – desympathized.

parameters were unchanged. The increase in CI and SV in IR could take place by a reflex mechanism, in response to vasodilatation and to an increase in the venous return [5]. The more marked reduction of TPVR in IR can be explained by lowering of the sympathetic tone of the vessels as a result of exposure of the CNS or peripheral autonomic pathways to particular factors (hyperosmolarity, glucose, and glucagon) [8, 11]. Lowering of TPVR in DR can be explained by the direct vasodilating action of humoral factors secreted into the blood stream after injection of STZ and/or by a decrease in sensitivity of the vascular smooth-muscle cells to humoral vasoconstrictor influences [3, 4, 6].

The principal result of these experiments, it must be considered, is therefore discovery of systemic vasodilatation only 24 h after injection of STZ, and also elevation of SV and CI in IR. This change in the parameters of the systemic hemodynamics may lead to an increased blood flow and to capillary hypertension in some vascular regions and, consequently, it may be a pathogenetic factor in the development of diabetic microangiopathies.

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