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Ornithine Carbamoyl Transferase as an Index of Severity in Hemorrhagic Shock[1] (37821)

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(Introduced by B. W. Zweifach)

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Lactic acid and uric acid are currently accepted as reliable indices of severity in hemorrhagic shock (1, 2). However, the almost ubiquitous availability of these substances in the body led us to search for another index with a more specific value. Since there are indications that the performance of the canine liver may be severely affected during hemorrhagic shock, we decided to study in addition the plasma ornithine carbamoyl transferase (OCT) activity during hemorrhagic shock in view of recent reports emphasizing its high degree of hepatic specificity (3, 4).

Method. Twenty dogs were studied in nembutal anesthesia (30 mg/kg). A "single withdrawal" hemorrhage model was used based partially on the experiences described by Ehrlich *et al.* (5) and Schmidt and Schmier (6). After a 30-min control period, the animals were bled to 40 mm Hg with 37.5% of the calculated blood volume being withdrawn. In order to fulfill both criteria, the initial withdrawal rate of 30 ml/min was altered after reaching about 20% of the calculated blood volume. It was increased if the arterial blood pressure came close to the 40 mm Hg level, and the withdrawal rate was slowed down if the arterial blood pressure was not yet close to this level. After fulfilling both criteria (40 mm Hg and 37.5% of CBV), the withdrawal line was disconnected and the arterial blood pressure was left uninfluenced. After having reached a certain maximum value ($P_{a,max}$) it started to decline again. In the first group of experiments, retransfusion was started after the arterial blood pressure dropped 20% from $P_{a,max}$ ("reversible" series); in the second series of experiments ("irreversible" series), retransfusion was started after the arterial blood pressure dropped 40% from $P_{a,max}$. Arterial blood pressure was recorded, and blood samples were taken to study plasma protein concentration measured by ultraviolet absorption at 280 nm, lactic acid (7), uric acid (8), and finally, ornithine carbamoyl transferase (OCT) (9). Blood samples were taken during the control period (C) (prior to hemorrhage), 20 min after termination of blood withdrawal (H_1), at the height of compensation (H_2), before retransfusion (H_3), and 20 min after completed retransfusion (T_1). In the "reversible" group, the T_2 sample was taken 1.5 hr after retransfusion, T_3 was taken 3 hr after retransfusion, and T_4 was taken prior to the termination of the observation period (6 hr after hemorrhage). In the "irreversible" shock group, the T_2 sample was taken after the arterial pressure started to decline again, the T_3 at 20%, and T_4 at 40% level of the peak P_a response. The amount of blood withdrawn for samples was immediately replaced by Dextran (Rheomacrodex).

Results. "Reversible" group. In the first group of experiments (7 dogs) in which shed blood was retransfused at 20% of $P_{a,max}$ (Fig. 1), 6 animals (85.5%) survived a 6-hr observation period ("reversible" group). The levels of uric acid, lactic acid,

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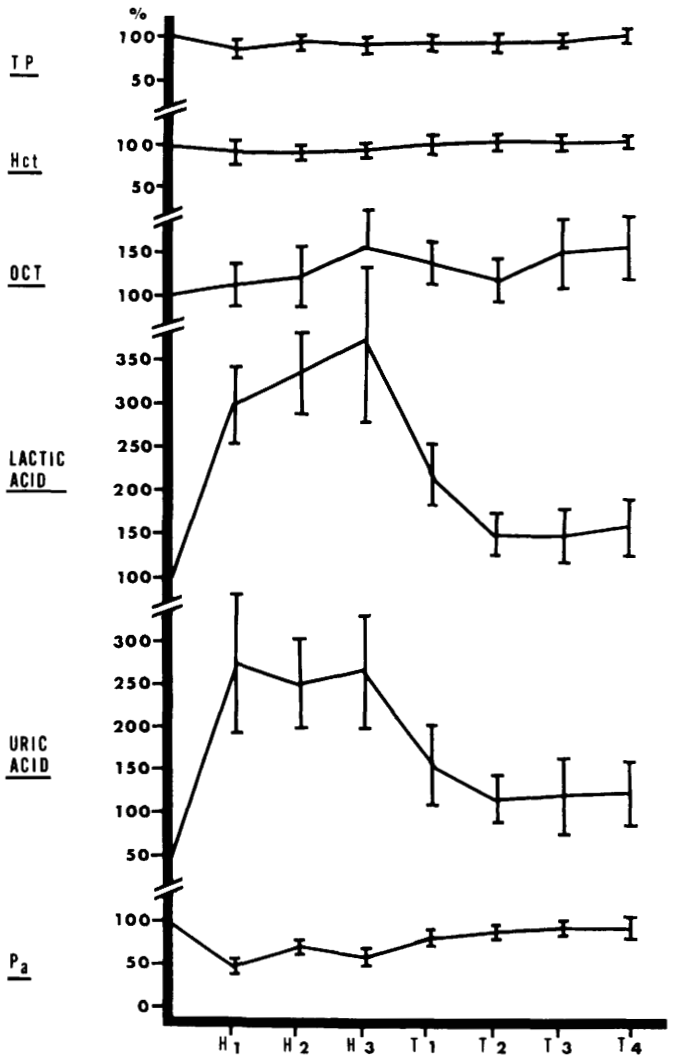

FIG. 1. Reversible shock (% changes). TP, Total proteins; Hct, hematocrit; OCT, ornithine carbamoyl transferase; P_a, arterial blood pressure. Absolute values (control) in Table I. Vertical bars indicate standard error of the mean.

and OCT decreased in the posttransfusion period after reaching a peak prior to retransfusion. They did not, however, reach the prehemorrhage control levels. Plasma protein concentration remained below the control values till the end of the observation period, although there was a tendency in the posttransfusion period to reach the initial value.

"Irreversible" group. In the second group of 13 dogs, the retransfusion was performed after the arterial blood pressure reached 40% of $P_{a,max}$. In this group, 11 animals (84.5%) did not survive the above-listed observation period. Actually, the average survival time (from H_1) in this group was 147.6 min (±84.0 SD). This group displayed significant differences in almost all of the investigated parameters (Fig. 2). To begin with, plasma protein concentration did not drop below the control value during the posttransfusion period. As expected, significant increases were observed in lactic and uric acid concentration. However, the most striking increase was observed in the OCT activity, especially in the late posttransfusion period which can be considered as the "irre-

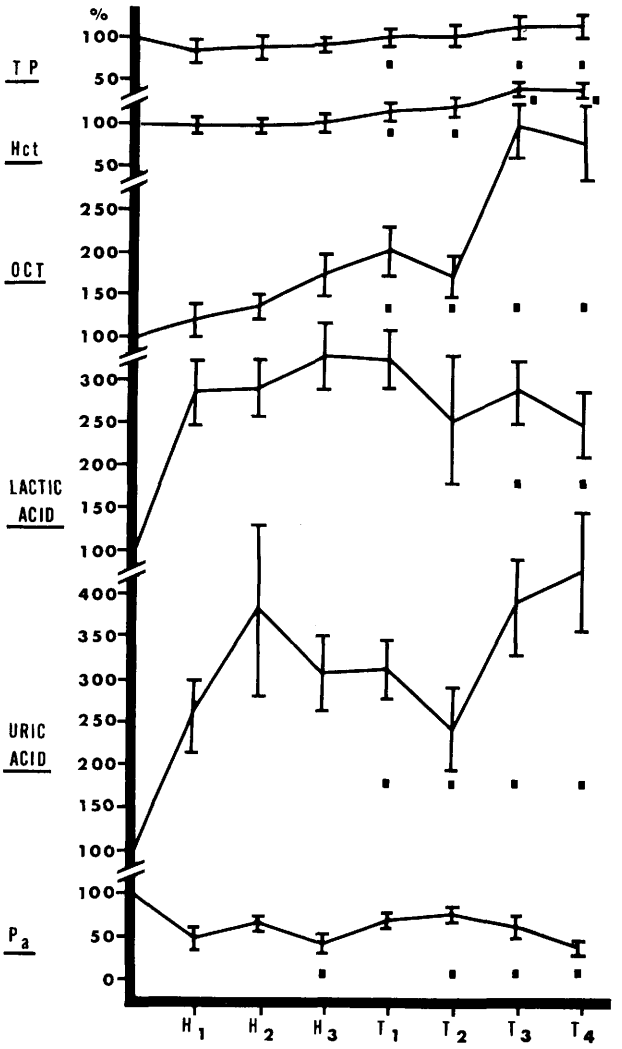

FIG. 2. Irreversible shock (% changes). Legend as in Fig. 1. Absolute values (control) in Table I. ■ indicates statistically significant difference ($P < 0.01$) as compared to the corresponding value in the "reversible" group.

versible" phase. The statistical significances are given in the respective figures.

Discussion. The described "single withdrawal" technique seems to represent a good model of hemorrhagic shock, since it comes closer to clinical reality than the classical continuous-withdrawal technique described by Wiggers (10), and, in addition, it offers an opportunity to study the animal's homeostatic mechanisms without being continuously interfered with by the equalizing reservoir. The increase in plasma protein concentration in the posttransfusion period is indirect evidence of the well-known loss of intravascular fluids (11–13) observed in canine hemorrhagic shock experiments. The highly significant increase in OCT activity can be interpreted as evidence of a relatively early specific impairment of hepatic functions, since OCT occurs mainly in the liver and to a far smaller extent in the small intestine (4). Krebs and coworkers (14) could not detect this enzyme in other organs. Reichard (15) has shown that 1 g of

TABLE I. Initial (Control) Values in Both Experimental Series.[a]

	"Reversible"		"Irreversible"	
	Control	SEM	Control	SEM
Uric acid (mg %)	0.69	0.08	0.84	0.17
Lactic Acid (mg %)	14.6	2.86	18.2	3.17
OCT (nmoles/ml/min)	32.0	6.71	20.3	5.08
Total Plasma Protein (g %)	7.10	0.60	7.16	0.35
Art. Blood Pressure (mm Hg)	135.3	9.00	125.9	4.14
Hematocrit (Vol. %)	39.0	2.22	41.1	1.28

[a] No statistically significant difference between the two control groups ($P < 0.01$).

liver tissue has approximately the same OCT content as 7 g of the small intestine. He concluded, therefore, that significant OCT serum elevations may be related mainly to liver cell damage and to a small extent to small intestine cell damage. Clinical experience has confirmed that an increase in OCT activity is observed almost specifically in patients with liver cell damage (4). Future experiments on different animals will demonstrate if this increase in OCT activity during hemorrhagic shock is confined to the canine species only, in view of some specific responses of the hepatic circulation in dogs during hemorrhagic shock (16, 17). Ultimately, clinical tests under equivalent conditions may determine its diagnostic value.

Summary. Hemorrhagic shock experiments were performed on 20 dogs divided into a "reversible" and "irreversible" series. Besides the conventional hemodynamic functions, the following metabolic indices were measured: lactic and uric acids, total proteins, and ornithine carbamoyl transferase (OCT). Under the described standardized experimental conditions (retransfusion after the posthemorrhagic arterial blood pressure dropped by 20%), 85.5% of the experimental animals survived a 6-hr observation period ("reversible" series). If the shed blood was retransfused after the arterial pressure dropped by 40%, 84.5% of the animals died within the same period of time ("irreversible" series). It has been shown that under the described experimental conditions, the increase in OCT activity is a very sensitive indicator of the degree of severity of shock. The species specificity of this index and its potential diagnostic value will have to be demonstrated.

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