EFFECT OF THE SEVERITY OF THE TERMINAL STATE ON ENDOCRINE GLAND FUNCTION IN THE EARLY PERIOD AFTER RESUSCITATION

A. V. Volkov, A. F. Bunatyan, T. I. Lukicheva
N. M. Efremova, and S. A. Meshcheryakova

UDC 616-036.882-08-036.8:616.43-008.6-072.7

The functions of certain endocrine glands were compared in the early period of resuscitation after clinical death from acute blood loss lasting 2, 8, and 10 min in experiments on dogs. To prevent hypovolemia, dextran was injected in repeated small doses. Regardless of the duration of clinical death, for a period of 9 h after resuscitation the activity of the components of the sympathico-adrenal system showed phasic changes of similar type. In dogs resuscitated after clinical death lasting 8 and 10 min, the plasma glucocorticoid level was maintained throughout the period of investigation at a much higher level than after clinical death lasting 2 min, while the adrenocorticotropic function of the pituitary was weakened; less marked inhibition of thyroid function of phasic changes in the plasma protein-bound iodine concentration were observed.

Hypoxia during the terminal state leads to profound disturbances of the functions of all organs and systems of the body, the severity of which rises with an increase in the duration of clinical death. These disorders subsequently determine the course of recovery during resuscitation and its outcome.

The disturbances of endocrine gland activity in the period after resuscitation have not yet been adequately studied.

The object of this investigation was to study reactions of the thyroid gland and of the sympathico-adrenal and hypophysio-adrenal systems in the early period of resuscitation after short and prolonged clinical death.

EXPERIMENTAL METHOD

Altogether three groups of experiments were carried out on 23 dogs. The terminal state was produced by acute blood loss. The animals were resuscitated by Negovskii's method [9]: in six experiments after clinical death lasting 2 min (group 1), in 11 experiments – 8 min (group 2), and in six experiments – 10 min (group 3). The experiments of groups 1 and 3 were carried out between November and January, and those of group 2 between February and May. Samples of arterial blood for the estimation of ACTH [8], total and biologically active forms of 11-hydroxycorticosteroids (11-HCS) [10], catecholamines [7], and protein-bound iodine (PBI) [11], were taken before the beginning of bleeding and in the period after resuscitation: after restoration of the corneal reflexes and 1, 6, and 9 h thereafter. The volume of blood lost through the taking of blood samples was replaced by dextran. After the 9-h sample, an additional 150-200 ml dextran was injected intravenously, so that its total content was 35-40 ml/kg. The hematocrit index in the last sample was reduced on the average by 15.7% ($P < 0.02$) compared with the initial level.

Laboratory of Experimental Physiology of Resuscitation, Academy of Medical Sciences of the USSR, Moscow. Interclinical Hormonal Laboratory, First Moscow Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR P. D. Gorizontov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 75, No. 4, pp. 20-24, April, 1973. Original article submitted March 17, 1972.

TABLE 1. Changes in Hormone Concentration (M ± m) in Plasma in Early Period of Resuscitation After Clinical Death of Different Duration

Index	Group	Number of experiments	Hormone concentration				
			before beginning of bleeding	in recovery period			
				restoration of corneal reflexes	1 h	6 h	9 h
Adrenalin in plasma (in μg ‰)	1	6	1,84±0,66	1,58±0,47	1,12±0,45	0,88±0,25	1,53±0,43 [5]
	2	11	1,30±0,38 [10]	1,32±0,39	2,93±1,16	1,87±0,53	1,17±0,56 [9]
	3	6	1,90±0,49 [3]	0,56±0,40 [4]	1,17±1,16 [3]	1,22±0,71 [4]	2,08±0,61 [4]
Noradrenalin in plasma (in μg	1	6	1,05±0,67	1,50±1,22	2,86±1,46 [5]	0,23±0,15 [5]	0,69±0,46
	2	11	1,84±0,75 [10]	2,84±0,80	1,94±0,76	0,52±0,35	0,60±0,39 [8]
	3	6	1,99±1,04 [3]	1,36±0,68 [4]	4,40±2,21 [3]	0,68±0,41 [4]	0,52±0,31 [4]
ACTH in blood (in μg %)	1	6	747±238	1283±469	1933±694	933±258	2535±881
	2	11	456±105	496±111 [9]	565±133*	964±213	1522±262
	3	6	773±290	728±99	725±111	760±96 [5]	1108±315 [4]
Total 11-HCS in plasma (in μg %)	1	6	23,2±4,8	19,6±3,0	18,2±3,6	17,4±4,4 [5]	16,3±1,4 [5]
	2	11	43,2±3,9*	36,2±3,0*	33,3±2,7*	33,4±2,7* [10]	35,6±4,1*
	3	6	27,8±2,5*	38,8±4,2*	39,0±3,4*	34,8±2,8*	27,7±2,3*
Biologically active 11-HCS in plasma (in μg %)	1	6	8,8±2,7	7,1±2,0	7,0±1,9 ‡	5,5±1,6 [5]	4,0±0,6 ‡ [5]
	2	11	18,4±2,0*	13,2±1,6*	9,1±0,9 [9]	11,6±1,5* [9]	14,9±1,7* [7]
	3	6	8,8±1,3 †	16,6±2,8*	17,2±2,6†	13,0±1,7*	8,2±1,2†
PBI in plasma (in μg %)	1	6	2,28±0,60	0,97±0,17	0,88±0,20	0,71±0,24	0,85±0,16
	2	11	3,64±0,91	1,22±0,22‡	1,96±0,74	1,83±0,70	2,39±0,74* [9]
	3	6	3,32±1,57	6,24±2,40*	5,70±2,48*	0,92±0,28 [5]	3,98±1,74

* Difference significant ($P < 0.05$) compared with figures for group 1.
† Difference significant compared with figures for group 2.
‡ Difference significant compared with figures for group 3.

EXPERIMENTAL RESULTS

The duration of the period of agony (9.8 ± 1.4, 12 ± 1.7, and 10.3 ± 0.8 min) and the volume of blood loss (68 ± 5; 80 ± 4; 81 ± 6%) leading to death, did not differ significantly in the 3 groups. Restoration of the vital functions took place more rapidly as the result of resuscitation after clinical death lasting 2 min than after clinical death lasting 8 and 10 min. With an increase in the period of clinical death, among the surviving dogs incomplete restoration of cerebral cortical functions was observed in one half of the cases (in five of nine surviving dogs of group 2 and in three of five surviving dogs of group 3). Three of the 17 dogs of groups 2 and 3 died after resuscitation.

The intensity and character of responses of the sympathico-adrenal system to the experimental preparations (immobilization of the animals, dissection of the blood vessels, and so on), just as in the period after resuscitation, showed no significant difference in the dogs of the different groups (Table 1). In animals of all groups 10-20 or 60 min after resuscitation the plasma noradrenalin concentration was increased, whereas the adrenalin level was increased only in some animals of group 2. A decrease in the total plasma catecholamine concentration was observed after 6 h ($P = 0.05$), mainly on account of noradrenalin. Activity of the adrenal component of the system began to predominate 6 and 9 h after resuscitation. In the present experiments there was no sign that prolonged activation of the sympathicoadrenal system observed previously [2] between 9 and 12 h after resuscitation from clinical death lasting 7 min. The reason was evidently connected with the beneficial action of dextran on the circulation by preventing the posthypoxic effusion of plasma into the intercellular space [4, 15, 16].

In all groups of experiments a high plasma 11-HCS concentration was observed before the beginning of bleeding. In the animals of group 2 the plasma 11-HCS concentration was considerably higher and the blood ACTH level lower than in dogs of the other groups. After clinical death lasting 2 min (group 1) the plasma 11-HCS concentration fell slowly when tested over a period of 9 h. The blood ACTH concentration was 2.6 times higher ($P = 0.05$) 1 h after resuscitation, it fell insignificantly toward 6 h, and 9 h after resuscitation it rose again to reach a level 3.4 times higher than initially. The increase in the ACTH level in the initial period of resuscitation, in the absence of a simultaneous reaction of 11-HCS, suggested predominance of extraadrenal effects of ACTH at this time and, in particular, inhibition of corticosteroid metabolism and an increase in the volume of their distribution [12, 14].

After clinical death lasting 8 min (group 2) the plasma concentration of total 11-HCS fell after 1 and 6 h to 77% of the initial level, and the concentration of biologically active 11-HCS fell to 49 and 63%, respectively ($P < 0.05$). After 9 h the 11-HCS concentration did not differ significantly from that initally. The blood ACTH concentration showed a tendency to rise 6 h after resuscitation, while after 9 h it was 3.3 times above its initial level ($P < 0.05$).

By contrast, after clinical death lasting 10 min (group 3) the plasma total 11-HCS concentration was increased by 40% after 20 and 60 min, and the concentration of biologically active forms was increased by 89 and 95% compared with that initially ($P < 0.05$). Later, toward 9 h, the 11-HCS concentration fell to its initial level. The blood ACTH concentration showed no significant change during the period of investigation, and 9 h after the beginning of resuscitation it was only 1.4 times higher than initially. The absence of changes in the ACTH concentration during elevation of 11-HCS level in the initial period of resuscitation could be evidence of posthypoxic disturbances of pituitary adrenocorticotropic function and of the predominance of parahypophyseal pathways of adrenocortical activation at that time. The fact that the changes in the plasma 11-HCS concentration were opposite in direction in the animals of groups 2 and 3 was evidently due to differences in the initial reactivity of the adrenal cortex. Meanwhile, in the dogs of groups 2 and 3 the plasma 11-HCS concentration at all stages of resuscitation was 1.5-3.5 times higher than in the animals of group 1; this was presumably because of, first, the greater activation of the adrenal cortex and, second, changes in the distribution of hormones in the body, in their metabolism, and in their excretion after prolonged clinical death. Disturbances of pituitary regulation of the adrenal cortex were found after clinical death lasting 10 min.

Judging from changes in the plasma PBI concentration (Table 1), after clinical death lasting 2 min thyroid function was deeply inhibited even in the initial stage of resuscitation ($P < 0.05$), and this inhibition persisted throughout the investigation; i.e., a response typical of the state of stress in normothermia was found [13]. After clinical death lasting 8 min, the decrease in the PBI concentration was less marked, while after clinical death lasting 10 min the plasma PBI concentration was increased for 1 h, decreased below the initial level after 6 h, and again increased after 9 h ($P < 0.05$). The possibility cannot be ruled out that the

increase in the PBI level in the initial period of resuscitation in the animals of group 3 was responsible for the simultaneous increase in the 11-HCS concentration [5, 6].

After long periods of clinical death (groups 2 and 3) the plasma glucocorticoid concentration was thus maintained at a higher level than after brief clinical death (group 1), while the adrenocorticotropic function of the adenohypophysis was weakened. A less marked inhibition of the thyroid or phasic changes in the plasma PBI concentration were observed. When dextran was injected to prevent hypovolemia in the period after resuscitation, no prolonged activation of the sympathico-adrenal system, such as was observed previously [2], occurred. Regardless of the duration of clinical death, for 1 h after resuscitation activation of the sympathetic component of the system was observed, followed by a decrease in the plasma noradrenalin concentration after 6 and 9 h and some degree of predominance of activity of the adrenal component at these stages. The protective-compensatory and pathological significance of the changes observed are confirmed by the results of simulation of endocrine responses in the period after resuscitation. A significant improvement in the results of resuscitation after prolonged clinical death has been obtained by giving ACTH and cortisol from the beginning of resuscitation [1, 9] and also in cases of prevention of prolonged activation of the thyroid gland [9, 17] and of the sympathico-adrenal system [3].

LITERATURE CITED

1. A. V. Volkov, The Glucocorticoid Function of the Adrenal Cortex and the Outcome of Resuscitation. Candidate's Dissertation, Moscow (1966).
2. A. V. Volkov and V. L. Kozhura, Pat. Fiziol., No. 6, 22 (1968).
3. A. V. Volkov and V. L. Kozhura, Farmakol. i Toksikol., No. 4, 422 (1970).
4. E. S. Zolotokrylina and S. S. Chistyakov, Probl. Gematol., No. 8, 32 (1965).
5. I. V. Komissarenko, in: Problems in Endocrinology and Metabolism [in Russian], Kiev (1970), p. 137.
6. M. A. Larina, The Biosynthesis of Corticosteroids in the Adrenals of Rabbits with Experimental Thyrotoxicosis. Candidate's Dissertation, Moscow (1962).
7. E. Sh. Matlina, Publications on New Apparatus and Methods [in Russian], No. 3, First Moscow Medical Institute, Moscow (1965), p. 84.
8. S. A. Meshcheryakova, Publications on New Apparatus and Methods, No. 8 [in Russian], First Moscow Medical Institute, Moscow (1969), p. 5.
9. V. A. Negovskii, Current Problems in Reanimatology [in Russian], Moscow (1971).
10. L. V. Pavlikhina, I. Ya. Usvatova, and A. F. Bunatyan, Publications on New Apparatus and Methods, No. 5 [in Russian], First Moscow Medical Institute, Moscow (1967), p. 50.
11. G. S. Stepanov, Lab. Delo, No. 10, 594 (1965).
12. D. L. Berliner, N. Keller, and T. Dougherty, Endocrinology, 68, 621 (1961).
13. K. E. Dewhurst, D. J. El Kabir, G. W. Harris, et al., Confin. Neurol. (Basel), 30, 161 (1968).
14. Kusama Mitsuhoshi et al., J. Clin. Endocrinol., 30, 778 (1970).
15. R. C. Lillehei, J. K. Longerbeam, J. H. Bloch, et al., Ann. Surg., 160, 682 (1964).
16. B. F. Bush and R. Morehouse, Surgery, 62, 188 (1967).
17. I. Voss and H. R. Schoen, Thoraxchir. Vask. Chir., 13, 3 (1965).