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Is Acute Failure of Adrenals an Important Factor Limiting Recovery from Cerebral Ischemia?

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Systemic arterial hypotension is a well-known factor limiting recovery from cerebral ischemia. The majority of studies have mentioned its noxious effect on reperfusion of cerebral microcirculation and have dealt with methods of counteracting it rather than with its mechanism. Several authors assume an impairment of the vasomotor centers in midbrain and hypothalamus as a basic event in the mechanism of hypotension (1,2,9). The necessity of pharmacological support of blood pressure during the hypotensive period in the extensive research on complete cerebral ischemia by means of several experimental models turned our attention to the possible role of the lack of endogenic vasopressor substances, among other reasons.

The purpose of this study was to characterize alterations of systemic arterial pressure during and after complete cerebral ischemia, and to correlate them with changes of noradrenaline concentration in the blood, as well as to analyze other factors participating in the mechanisms of ischemic-postischemic hypotension.

MATERIAL AND METHODS

The experiments were carried out under i.v. pentobarbital anesthesia, 35 mg/kg, in 76 adult rabbits of both sexes. Complete cerebral ischemia was produced by two experimental models: compressive ischemia of 5 to 15 min duration, described by Kawakami and Hossman (7), and occlusive ischemia up to 60 min, described by Hossmann and Zimmermann (6). In both models, animals were tracheotomized, and ventilated with room air; however, in the second model, they were immobilized with gallamine triethiodide (Tricuran), and occlusion of arteries supplying the brain was performed suprasternally without thoracotomy (13). Additionally, a 30 min cerebral ischemia was produced in nine Mongolian gerbils under intraperitoneal anesthesia, 70 mg/kg, by bilateral occlusion of the common carotid artery with supportive controlled ventilation. The following parameters were recorded continuously and/or periodically. In rabbits and gerbils, an electrocorticogram (ECoG) and an electrocardiogram with a second limbic lead (EKG) were taken, and systemic arterial pressure from the femoral artery (SAP) was monitored. In rabbits, the integrated bioelectric activity of the respiratory centers from the phrenic nerve was measured, and cerebral blood flow was measured by means of the ^{133}Xe washout technique. Intracranial pressure from the

cisterna magna, blood gases and pH, endtidal CO_2, and rectal temperature were monitored. The whole blood concentration of noradrenaline (NA) and adrenaline were determined by means of spectrofluorometric assay after chromatographic separation (11). The experiments in rabbits were carried out under suppression of hypertensive response by means of the ganglioblocking agent trimethaphan camphosulfonate (Arfonad) and/or bloodletting; however, in 16 animals, the above procedure was postponed to get a pure experimental picture of "sympathetic discharge." Differences between mean values of NA concentration in the blood were assessed by Student's *t*-test for unpaired data. Survival time of animals was up to 6 hr, after which postmortem gross examination and light microscopic studies were performed, including the brain, heart, lungs, and adrenals.

RESULTS

In both experimental models in rabbits, complete cerebral ischemia triggered immediate hypertensive response, which developed in the first minute of ischemia (Figs. 1 and 2). The rise of blood pressure was more steep in compressive than in occlusive ischemia. An increase of SAP in compressive ischemia amounted to 70.0 ± 10.7 mm Hg (n = 8), and in occlusive ischemia to 62.0 ± 10.7 mm Hg (n = 8). In animals without suppression of vasopressor response, extrasystolic cardiac arrhythmia was present as a rule at the top of the blood pressure rise.

An increase of blood pressure was observed also in gerbils after bilateral occlusion of the common carotid artery. However, rise of blood pressure in these animals was very slow (the highest pressure occurred between 3 and 12 min after occlusion) and amounted to 28.0 ± 9.7 mm Hg (n = 9). No cardiac arrhythmia was observed during the hypertensive period.

The sequence of blood pressure changes in rabbits during and after complete cerebral ischemia in both experimental models without suppression of vasopressor response is presented in Figs. 3 and 4. Systemic arterial pressure began to decrease below the control values at 4.0 ± 0.8 min of ischemia in the compressive model (n = 8), and at 3.6 ± 0.9 min in the occlusive model (n = 8). A maximum decrease of blood pressure as compared to the control values amounted to 48.0 ± 8.1 mm Hg in the first model, and to 60.0 ± 11.0 mm Hg in the second model. The lowest level of blood pressure appeared at 6.1 ± 1.3 min in the compressive model (n = 7), and at 12.1 ± 8.3 min in the occlusive model (n = 7). In a majority of cases, an early decrease of blood pressure below the control values in both experimental models was related to disturbances of cardiac function.

Analysis of blood pressure changes in rabbits with suppression of vasopressor response by means of Arfonad and/or bloodletting, i.e., without disturbances of the cardiac function in two experimental models (15 min compressive ischemia; 30 min occlusive ischemia), gave the following results. Systemic arterial pressure began to decrease below the control values at 8.2 ± 2.4 min of ischemia (n = 11) in the compressive model, and it began to decrease below the predicted 75 mm Hg at 3.8 ± 0.9 min of ischemia (n = 11) in the occlusive model. The lowest level of blood pressure, below which it was necessary to support SAP by means of vasoactive drugs, appeared at 8.8 ± 2.8 min of ischemia in the first model (n = 8), and at 11.8 ± 4.1 min of ischemia in the second model (n = 10).

In gerbils, after bilateral carotid occlusion, no arterial hypotension was observed throughout the whole 30 min period of cerebral ischemia. On the contrary, during the first 15 min of ischemia, the blood pressure was in the majority of cases higher than control.

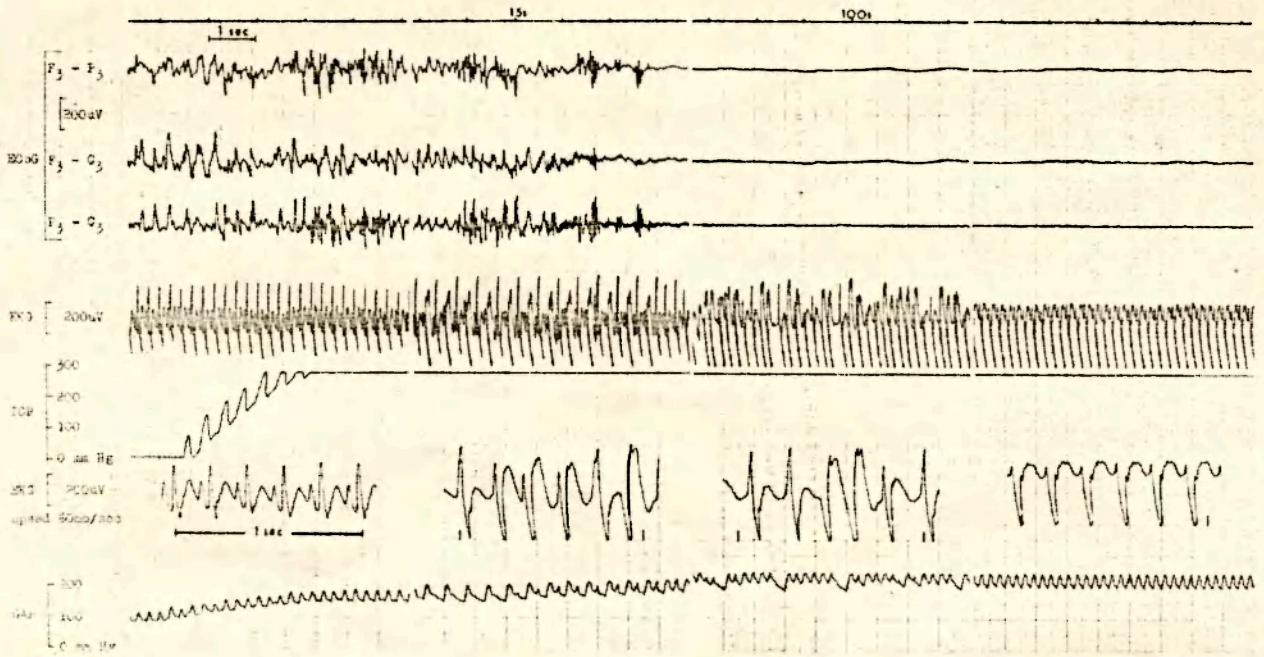

FIG. 1. Hypertensive response to complete cerebral compressive ischemia in the rabbit. At the height of the blood pressure rise, cardiac arrhythmia with missing beats is seen, followed by ventricular tachycardia. ECoG, electrocorticogram; EKG, electrocardiogram; ICP, intracranial pressure; SAP, systemic arterial pressure.

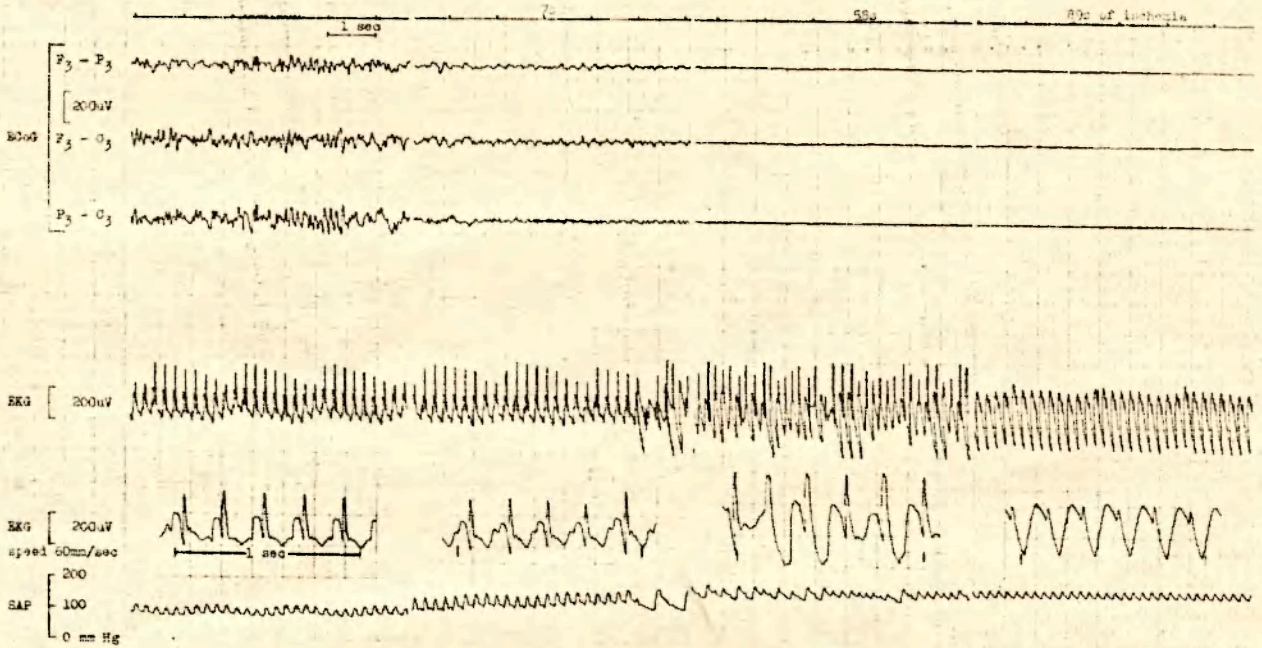

FIG. 2. Hypertensive response to complete cerebral occlusive ischemia in the rabbit. At the height of the blood pressure rise, cardiac arrhythmia with missing beats is seen followed by ventricular tachycardia. ECoG, electrocorticogram; EKG, electrocardiogram; SAP, systemic arterial pressure.

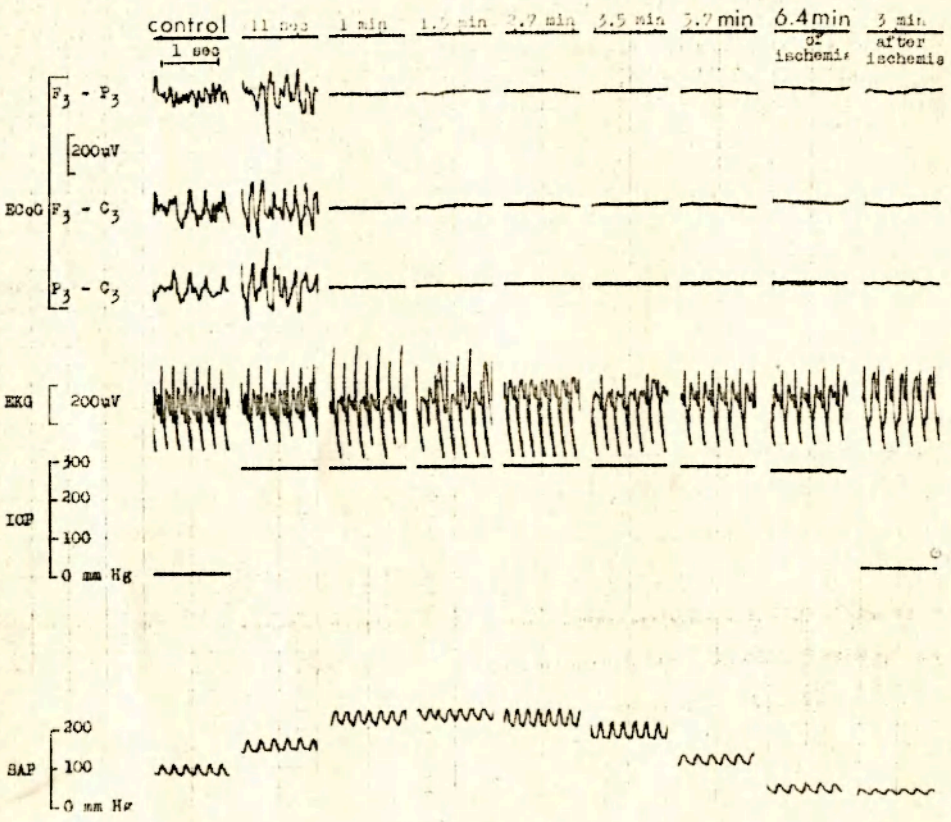

FIG. 3. Sequence of blood pressure changes during and after 10 min complete cerebral compressive ischemia in the rabbit. Experiment without ganglioblocking suppression of vasopressor response and bloodletting. Note progressing deterioration of the cardiac function. ECoG, electrocorticogram; EKG, electrocardiogram; ICP, intracranial pressure; SAP, systemic arterial pressure.

Irrespective of the experimental model applied, cessation of cerebral ischemia produced in all animals a brief but profound drop of blood pressure, which had to be treated in some cases with vasoactive drugs. Blood NA concentrations in rabbits during and after cerebral ischemia in both experimental models are presented in Figs. 5 and 6.

In occlusive ischemia, during the first minute of the ischemic period, NA concentration rose significantly from the control level of 1.81 ± 0.59 ng/ml (n = 11) to 4.80 ± 2.05 ng/ml (n = 7), $p < 0.001$, and decreased to 2.85 ± 2.19 ng/ml (n = 7) during the 18th minute of ischemia, whereas in the third minute after ischemia, it dropped to 1.59 ± 1.12 ng/ml (n = 5), which is insignificantly below control.

In compressive ischemia, the blood NA concentration rose significantly during the first minute of the ischemic period from a control level of 1.17 ± 0.95 ng/ml (n = 16) to

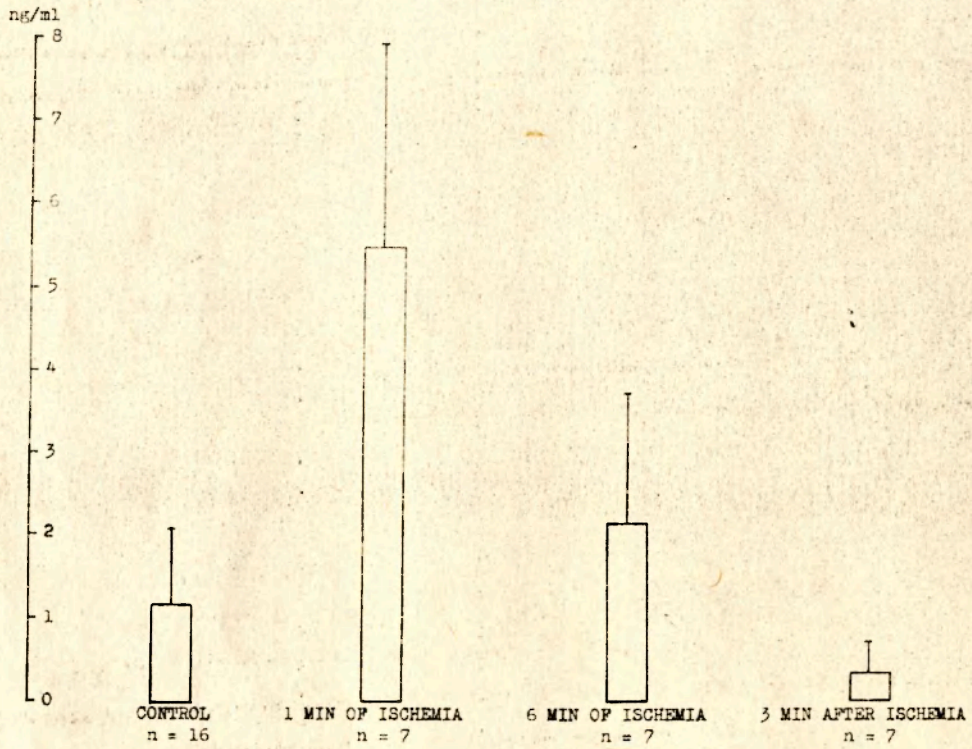

FIG. 6. Blood noradrenaline concentration during and after 10 min complete compressive ischemia of the rabbit brain. Experiments without ganglioblocking suppression of vasopressor response and bloodletting. Mean ± SD; *n* = number of animals.

vasopressor response, severe cardiac disturbances developed during cerebral ischemia, leading in majority of cases to the left heart failure and pulmonary edema. The results of these observations were published elsewhere (8).

The second hypotensive period is much more complicated in its possible pathomechanisms, and was not explored as thoroughly as the Cushing's reflex. It should be stressed that the above pathological state develops in all animals with complete cerebral ischemia, including those in which the vasopressor response is suppressed by means of ganglioblocking agents and/or bloodletting. The early decrease of blood pressure up to the 7th to 8th minute of ischemia is not to be defined as actual arterial hypotension, since there are many reasons for it, such as different reactivity of animals to ganglioblocking agents, speed of bloodletting and reinfusion, periodical impairment of cardiac function, and others. However, our results clearly showed that between the 9th and 12th minute of complete cerebral ischemia, in whichever experimental model with rabbits, a genuine and marked hypotension developed, and SAP had to be supported by means of vasoactive drugs.

Despite the general similarity of changes in blood NA concentration in both experimental models, their mechanisms should be discussed separately.

Occlusive ischemia in the group of animals in which blood NA concentration was evaluated had been produced in conditions of suppression of vasopressor response by means of brief reversible bloodletting, and during the hypotensive period, blood pressure was supported by i.v. infusion of Hypertensin. This treatment resulted in the rise of NA concentration in

blood to the level of only 2.7 times that of control, and was followed by a relatively slow decrease to the control values in the postischemic period.

Compressive ischemia in the group of animals in which blood NA concentration was assayed had been produced in conditions of maximum sympathetic discharge, i.e., with no suppression of vasopressor response and bloodletting. This resulted in the rise of NA concentration to 4.7 times the control value, and subsequently to a relatively quick drop to a below control level during the postischemic period.

Since NA is secreted from the adrenal medulla, it seems reasonable to assume acute functional exhaustion of adrenals after sympathetic discharge. Our morphological examinations revealed numerous hemorrhagic foci in the adrenal cortex. The same pathological alterations in adrenals have been described by other authors in cats during intracranial hypertension (14).

Comparison of the blood pressure changes and blood NA concentration in the periods under examination showed a close correlation during the early ischemic period, and a discrepancy between these two parameters in the 18th minute of ischemia in the occlusive model and in the 6th minute in the compressive model, when still higher blood NA concentration coincided with the low blood pressure. Blood catecholamine concentration in a given period of time is a mean value between the secretion, excretion, and metabolic degradation; each may be very abnormal in pathological conditions.

Similar vasopressor response in compressive and occlusive cerebral ischemia in rabbits, and maximum rise of blood pressure during the beginning of respiratory disturbances in gerbils after bilateral carotid occlusion, supports the ischemia or hypoxia of medullary centers as the mechanism triggering sympathetic discharge, which operates through the medulloadrenal axis. Since an increase of blood noradrenaline concentration and blood pressure rise is higher in compressive than occlusive ischemia, the mechanism of local stimulation of the brainstem structures may well contribute to the overall mechanism of the vasopressor response.

When the vasopressor response is not suppressed, severe cardiac disturbances are developing, leading to the left heart failure and pulmonary edema. Between the 9th and 12th minute of complete cerebral ischemia, marked hypotension develops, and it is necessary to support blood pressure by means of exogenic vasopressor substances.

Though there is a close correlation between blood pressure changes and blood NA concentration during the early ischemic period and much less of a correlation in the later period, NA concentration progressively decreases from the highest value during the vasopressor response to below control during postischemic period following maximum sympathetic discharge. The lack of arterial hypotension in gerbils after bilateral carotid occlusion with supportive controlled ventilation, in conditions where the brain hemispheres are ischemic and the medulla is perfused, as well as the developing hypotension in complete cerebral ischemia, supports the notion that impairment of vasomotor centers is a basic event in the mechanism of hypotension. Nevertheless, acute failure of the adrenals may well contribute to the overall impairment of the neurohumoral control of the vascular resistance.

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