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Coagulopathy Following Experimental Cerebral Ischemia

KONSTANTIN-ALEXANDER HOSSMANN, M.D., PH.D. AND VOLKER HOSSMANN, M.D.

SUMMARY In adult normothermic cats cerebral blood flow was interrupted for 1 hour by clamping the innominate and subclavian arteries. Following ischemia the brains were recirculated with blood, and the coagulation system was investigated by measuring coagulation times and blood content of fibrinogen and platelets. Ischemia induced progressive consumption coagulopathy with an increase in coagulation times and a decrease of platelets and fibrinogen by more than 40%. Coagulopathy was accompanied by a respiratory distress syndrome with a significant increase in the alveolar-arterial carbon dioxide gradient from -3.3 to -13.5 mm Hg. A correlation was found between plasma fibrinogen concentration, cerebral blood flow and electrophysiological function, indicating that a relationship exists between the severity of postischemic coagulopathy and functional recovery following prolonged cerebral ischemia.

DISSEMINATED INTRAVASCULAR coagulation is a serious complication which accompanies various pathological conditions such as septicemia, intravascular hemolysis, endothelial damage, and severe shock. Less known is its occurrence in anoxia or ischemia, especially in that of the central nervous system. Following transient cerebral ischemia disseminated intravascular coagulation may interfere directly or indirectly with the recovery by means of three different mechanisms: a) impairing the microcirculation of the brain; b) producing pulmonary microembolization and c) eliciting reactive fibrinolysis. Microcirculatory disorders have been demonstrated to be of importance in the pathogenesis of the so called no-reflow phenomenon which is one of the limiting factors for recovery after prolonged cerebro-circulatory arrest. Pulmonary microembolization may cause a respiratory distress syndrome and reactive fibrinolysis bears the risk of promoting hemorrhagic infarction of the ischemic brain. In the present investigation the occurrence of disseminated intravascular coagulation was studied in animals which were subjected to one hour's complete selective ischemia of the brain. This experimental model has been used in our laboratory for the study of functional recovery after prolonged ischemia, and information is available on various physiological, biochemical and morphological aspects of the recovery process. The comparison of these data with the changes in coagulation parameters following ischemia indicates that disseminated intravascular coagulation may present a problem for the revival of the brain following cerebro-circulatory arrest.

Methods
Fifty adult cats were anesthetized with pentobarbital (30 mg/kg Nembutal® intraperitoneally), immobilized with
gallamine triethiodide (Flaxedil®) and mechanically ventilated with room air. End-tidal oxygen and carbon dioxide were continuously recorded and blood gases measured periodically using gas analyzers (Oxytest and Uras, Hartmann and Braun, Frankfurt; Mikro-Astrup, Copenhagen). The respiration was adjusted to yield a PaCO₂ of 28 to 30 mm Hg and a PaO₂ of more than 100 mm Hg.

Cerebro-circulatory arrest was produced by intrathoracic clamping of the innominate, the left subclavian, and both internal mammary arteries, combined with induced hypotension by a ganglioplegic agent (camphor sulfonate, Arfonad®). Recirculation of the ischemic brain was achieved by removing the clamps and raising the blood pressure with a sympathicomimetic drug (norfenefrin, Novadral®). Shifts in the acid-base and electrolyte balance of the blood were corrected by appropriate infusions of buffers and electrolyte solutions. Postischemic brain swelling was treated with hypertonic solutions.

Arterial blood samples were withdrawn prior to ischemia, at the end of 1 hour’s ischemia and at different recirculation times after ischemia using 10 vol % of a 0.1 mol sodium citrate solution as an anticoagulant. Recalcification time, prothrombin and thrombin times were measured at 37°C with a mechanical clot timer (Mechrolab, Heller Lab., Santa Rosa) using standard coagulation reagents (25 m mol calcium chloride, Test Thrombin®, and Calcium Thromboplastin®, Behringwerke, Marburg). Quantitative determination of fibrinogen was performed by inducing coagulation with a standard fibrinogen reagent (Boehringer, Mannheim).

Blood platelets were counted in hemolyzed blood samples using a phase contrast microscope. The effect of intravascular coagulation on pulmonary gas exchange was estimated by correlating end-tidal CO₂ with the CO₂ in the arterial blood. Cerebro-circulatory disturbances were detected by the conventional 133Xenon clearance technique, and in some animals by microscopic observation of the pial microcirculation.

In five animals the brains were removed at the end of the experiment, fixed in formalin and processed for light microscopy. Histological sections were stained with hematoxylineosin and by the Mallory-Heidenhain technique, and investigated for the occurrence of intravascular fibrin deposits. In addition, histological sections from 12 brains of an earlier experimental series with one hour’s ischemia18 were reviewed for the occurrence of hemorrhages.

Results

1. Coagulation Disturbances Following Cerebral Ischemia

Prior to ischemia the following control recordings were obtained: recalcification time was 125 ± 9.2 sec (means ± SE), prothrombin time was 12.5 ± 0.3 sec, thrombin time was 33.1 ± 2.1 sec, plasma fibrinogen concentration was 224 ± 15 mg %, and platelet count was 278000 ± 19200/mm³.

Cerebral ischemia initiated severe coagulation disturbances (figs. 1, 2). At the end of the ischemic period fibrinogen had decreased to 186 ± 18 mg % and platelets to 233000 ± 22500/mm³. Concomitantly, prothrombin time had lengthened to 16.4 ± 1.1 sec, thrombin time to 46.1 ± 3.0 sec, and recalcification time to 250 ± 30.1 sec. The changes were not due to variations in hematocrit which during ischemia increased slightly from 34.4 ± 0.81 to 35.3 ± 1.31 % (fig. 1).

In some animals a hypercoagulable state preceding consumption coagulopathy could be detected shortly after the beginning of ischemia. This state was characterized by a transient shortening of the coagulation times at normal or only slightly reduced fibrinogen levels.

When the blood flow to the brain was restored after

![Figure 1](https://stroke.ahajournals.org/content/8/2/250.f1)

**Figure 1.** Changes in fibrinogen, thrombocytes and hematocrit during and after 1 hour’s cerebral ischemia (means ± SE). Asterisks indicate statistical difference from control (n.s. not significant): *P < 0.05; **P < 0.01; ***P < 0.001.
ischemia, fibrinogen further decreased to 113 ± 15.0 mg% and platelets to 196,000 ± 2,160/mm³ within 30 min of recirculation. In some experiments even complete depletion of fibrinogen and platelets was observed. The consumption of fibrinogen was related to a further lengthening of the prothrombin and recalcification times; thrombin time remained at the same elevated level as during ischemia.

During the initial 30 min of recirculation the changes in the coagulation system were slightly exaggerated by post-ischemic hemodilution (fig. 1). Hemodilution, as evidenced by the decreased hematocrit value, arose as the consequence of the rapid infusion of buffers and plasma expanders which were used for the equilibration of postischemic acidosis and the stabilization of blood pressure. However, the low hematocrit was not the only reason for the disturbances in the coagulation system: at longer recirculation times hematocrit improved in contrast to coagulopathy which remained unchanged.

In two control experiments the participation of methodological factors in the development of coagulopathy was studied. In one animal extracerebral ischemia of 1 hour's duration was induced by cross-clamping the abdominal aorta using the same pharmacological treatment as in the main experimental group. In another experiment, only the pharmacological treatment was mimicked, i.e. hypotension of 1 hour was induced by camphor sulfonate followed by norfenefrin infusion, but without production of ischemia. The results demonstrate that only the abdominal clamping caused consumption coagulopathy which indicates that ischemia and not the pharmacological treatment was responsible for the observed changes in the coagulation system (fig. 3).

2. Effect of Coagulopathy on Cerebral Microcirculation

A quantitative evaluation was attempted by correlating cerebral blood flow with the concentration of fibrinogen 2 to 4 hours after ischemia. This time was chosen because coagulopathy was maximal after this interval, and because previous investigations had shown that at this time postischemic hyperemia had ceased. Consequently, disseminated intravascular coagulation should be reflected by a slowing of cerebral blood flow.

Figure 4 demonstrates that fibrinogen concentration correlated significantly with cerebral blood flow. However, intravital microscopical observations of the cortical surface and postmortem histological examination of the brains stained by the Mallory-Heidenhain technique did not reveal fibrin-platelet thrombi and intravascular fibrin deposits. It is, therefore, more likely that the observed decrease in blood flow was an indirect consequence of intravascular coagulation rather than the result of intravascular clots.

3. Consumption Coagulopathy and Cerebral Hemorrhage

In an earlier series comprising 12 cats with 1 hour's ischemia and consecutive recirculation brain histology was performed. This material was reviewed for the occurrence of postischemic cerebral hemorrhages.

In only 4 of these twelve cats were small hemorrhagic lesions present, most of them localized in the brain stem and the cerebellum. In 7 animals, circumscribed infarcts were seen in border zones between the main arterial territories of the hemispheres but none of these was hemorrhagic. In the cases with cerebellar and brain stem lesions, herniation arising from postischemic brain swelling was present; this suggests that the hemorrhagic lesions were more likely to be due to mechanical trauma than to afibrinogenic bleeding. Consumption coagulopathy in animal experiments does not promote hemorrhages therefore, unless traumatic lesions are present.
4. Effect of Coagulopathy on Pulmonary Function

Intravascular coagulation in pulmonary vessels induces pulmonary edema and atelectasis, resulting in an impairment of gas exchange in the lungs (pulmonary distress syndrome). The efficiency of pulmonary ventilation was estimated from the alveolar-arterial gradient in the partial pressure of carbon dioxide.

This gradient transitorily increased from $-3.3 \pm 0.68$ mm Hg at the beginning of the experiment to $-13.5 \pm 1.31$ mm Hg during the first hour of postischemic blood recirculation. At longer recirculation times it again decreased, indicating that respiratory insufficiency was partly reversible.

Pulmonary distress was also reflected by an impairment of arterial oxygenization. With the present experimental set-up the precise degree of this disturbance could not be evaluated, but we realized that oxygen content of the inspired air had to be increased up to 50% in order to maintain an arterial $P_{O_2}$ of more than 100 mm Hg.

5. Coagulopathy and Functional Recovery of the Brain

Functional recovery after ischemia was classified according to different electrophysiological parameters such as evoked responses and EEG activity. In 27 animals with electrophysiological recovery evoked responses began to reappear within 15 min, and spontaneous EEG activity within 3 hours of recirculation. In 21 animals without recovery these requirements were not fulfilled. In both groups distinct coagulopathy was present but in the animals without recovery fibrinogen was even significantly lower and thrombin time longer than in those with recovery (table 1).

An indirect consequence of the coagulopathy was the increase in the alveolar-arterial $CO_2$ gradient which was significantly higher in the animals without recovery. This and the positive correlation between blood flow and fibrinogen (see above) indicates that a direct relationship exists between the severity of postischemic coagulopathy and the quality of the electrophysiological recovery process after prolonged cerebral ischemia.

Discussion

The pathomechanism of disseminated intravascular coagulation has been most extensively studied in shock. It is induced by the combined effect of hypocirculation and acidosis with consequential platelet aggregation and activation of Hageman factor XII. Coagulation is further enhanced by procoagulants, fibrinolytic inhibitors, vasoactive substances, and blockage of the reticulo-endothelial system which results in diminished phagocytosis of breakdown products of fibrinogen and activated coagulation factors [for review see Ref. 3]. The increased turnover of the coagulation process is followed by secondary consumption coagulopathy which is characterized by a decrease in platelets and fibrinogen, and which may complicate the primary lesion by multiple hemorrhages.

Disseminated intravascular coagulation following cerebral ischemia has been much less investigated although indications of coagulation disturbances have been reported. 

**Figure 4. Correlation between plasma fibrinogen concentration and cerebral blood flow (CBF) following 1 hour's cerebral ischemia. Measurements were performed 2-3 hours after the beginning of recirculation.**

- $y = 0.08x + 18$
- $r = 0.71$
- $p < 0.01$
the brain following transient ischemia, and Hekmatpanah described an agglomeration of red cells and the formation of microemboli in pial arteries following cardiac arrest. Platelet aggregation and fibrinogen deposits in cerebral vessels have also been observed in animal experiments after clamping the aggregation and fibrinogen deposits in cerebral vessels have been observed in animal experiments after clamping the cerebral artery. Finally, Anderson and Brown concluded from pathological findings that in newborn children disseminated intravascular coagulation may be related to brain ischemia or hypoxia.

Our own finding of severe consumption coagulopathy following prolonged cerebral ischemia was consistent with these observations. The pathomechanism of this disturbance was presumably similar to that of shock with tissue acidosis and platelet aggregation being the most important factors. Catecholamines, which have been shown to activate coagulation in hypoxia, played a lesser role because the sympathico-adrenergic vasopressor response at the beginning of ischemia was blocked by a ganglioplegic agent. The therapeutic doses of catecholamines which were used for stabilization of blood pressure after ischemia were too low to evoke appreciable coagulopathy. However, the possibility of enhancing coagulopathy should be remembered when sympathicomimetics are used clinically.

The present investigation demonstrated a relationship between coagulopathy and the functional recovery process after ischemia. This relationship could have been purely coincidental because a greater degree of brain damage would yield both less functional recovery and a more prolonged stimulation of intravascular coagulation. On the other hand, coagulopathy could interfere directly with postischemic blood recirculation since a positive correlation was found between the decrease in plasma fibrinogen concentration and the reduction in blood flow.

This delayed impairment of blood flow is different from the so-called no-reflow phenomenon which appears immediately upon recirculation and is due to vascular obstructions in combination with an increased blood viscosity. In contrast, the delayed circulatory impairment seems to be a functional disturbance which develops after a preceding phase of hyperemia and which is due to arterial vasospasm. The vasospasms are possibly related to disseminated coagulation because serotonin, which is a potent vasoconstricting agent, is released from platelets during ischemia.

Another risk factor for functional recovery after ischemia is pulmonary insufficiency. It is well known that damage of the central nervous system may promote pulmonary distress. Pathophysiological factors which have been discussed before are destruction of hypothalamus, lesions of the preoptic area or activation of the sympathetic vaso-motor system. In the present experiment, ischemia per se induced small changes but there was a considerable impairment of pulmonary gas exchange immediately upon recirculation. It is more likely, therefore, that pulmonary distress was secondary to disseminated coagulation rather than the consequence of neurogenic activation.

Pulmonary distress and cerebro-circulatory impairment obviously will cause cerebral anoxia when not properly dealt with, and will thus interfere with postischemic recovery. This may explain why in earlier experiments fibrinolysis improved the functional outcome of an ischemic impact. In other investigations, however, a protective effect of anticoagulants has been denied. It therefore remains to be shown whether anticoagulation or symptomatic treatment of vasospasms and pulmonary distress is the more efficient way to deal with the harmful effects of postischemic coagulopathy.

**Acknowledgment**

The technical assistance of Miss I. Niebuhr is gratefully acknowledged.

**References**

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**Table 1** Comparison of Various Coagulation Parameters in Animals with and without Electroepileptological Recovery after Ischemia: Measurements Made Before (Control) and 2-3 Hours After Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Control (Mean ± SE)</th>
<th>Recovery (Mean ± SE)</th>
<th>No recovery (Mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recalcification time (sec)</td>
<td>12.5 ± 9.2</td>
<td>33.7 ± 24.5**</td>
<td>398 ± 49.7***</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>12.5 ± 0.3</td>
<td>20.2 ± 1.0**</td>
<td>23.3 ± 2.0**</td>
</tr>
<tr>
<td>Thrombin time (sec)</td>
<td>33.1 ± 2.1</td>
<td>45.8 ± 4.0**</td>
<td>57.4 ± 6.1**</td>
</tr>
<tr>
<td>Thrombocytes (x1000/mm³)</td>
<td>278 ± 19.2</td>
<td>180 ± 22.4**</td>
<td>122 ± 17.8**</td>
</tr>
<tr>
<td>Fibrinogen (mg/100ml)</td>
<td>224 ± 15</td>
<td>124 ± 15.0**</td>
<td>57.5 ± 13.2**</td>
</tr>
<tr>
<td>Hct (Vol%)</td>
<td>34.4 ± 0.8</td>
<td>32.1 ± 1.0*</td>
<td>29.4 ± 2.4</td>
</tr>
<tr>
<td>Alveolar-arterial CO₂ gradient (mm Hg)</td>
<td>-3.3 ± 0.7</td>
<td>-5.1 ± 0.8*</td>
<td>-8.9 ± 1.6**</td>
</tr>
</tbody>
</table>

Different from control group *P <0.05; **P <0.01; ***P <0.001; Different from animals with recovery P <0.05; §§ P <0.01.
Effects of High Static Pressures on Human Cerebral Arteries in Vitro

D. A. COPE, M.S.C. AND MARGOT R. ROACH, M.D., PH.D.

SUMMARY Static elastic properties were obtained from pressure, volume, and length measurements of 34 isolated human cerebral arteries from 23 circles of Willis of patients aged 23–76 years. No significant difference in initial or final elastance was observed with age or branch in the circle of Willis. Twenty-four of the arteries from 18 circles of Willis were then subjected to transmural pressures of 200–300 mm Hg for periods of ≤ 5 minutes and the elastic properties restudied. In general, this had little effect on the arteries except for a significant increase in the initial radius for the ≤ 40 year age group. In the ≤ 40 year group, female arteries tended to show a greater increase in initial elastance than the males. Histological studies to look for elastin fragmentation in the intima were inconclusive.

THERE IS INCREASING EVIDENCE that human intracranial saccular aneurysms are acquired rather than congenital. Hassler and Nystrom have both stressed the importance of elastin fragmentation in aneurysms, and it seems likely that a break in the internal elastic membrane at the apex of an intracranial bifurcation may be the factor which initiates the development of an aneurysm. While Ferguson and Roach postulated that some hemodynamic force caused the fragmentation, this has not been proven.

Scott et al. showed clearly that the elastic properties of human cerebral arteries and aneurysms were different, and that the elastin part of the curve (i.e. the low pressure part) was absent in aneurysms. They also found, in a few arteries, that repeating the pressure-volume curves more than three times appeared to change the elastic properties of the artery to elastic properties more like those of an aneurysm. Since all of their arteries were subjected to pressures of at least 200 mm Hg, they postulated that high pressures might fragment the elastin, but could not say what pressure, or what duration of high pressure cause this alteration. Fragmentation of the elastin was postulated to be associated both with an increase in initial radius, and also with a change in the initial slope of the tension-strain diagram.

Our experiments were designed to determine, if possible, whether pressure would fragment the elastin in isolated human cerebral arteries, and to determine if the age of the artery altered the response.

Methods

Thirty-four arteries were gently dissected from 23 circles of Willis of age 23–76 years at autopsy, and stored in saline at 4°C until use. Previous studies had demonstrated that the static elastic properties did not change for at least ten days under these conditions. All arteries were studied in less than one week after death.
Coagulopathy following experimental cerebral ischemia.
K A Hossmann and V Hossmann

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