Intravascular aggregation after acute intracranial hypertension by epidural balloon compression in cats

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The authors have studied the effect of acute intracranial hypertension produced by placement of an epidural balloon (control group) in cats, on cerebral perfusion, evoked responses, and hematological parameters. These elements were measured in similarly injured animals which underwent isovolemic hemodilution with dextran 75, after relief of intracranial hypertension. Four hours after balloon deflation, perfusion was markedly impaired in 30% of the control group, and was reduced to 11% in the dextran-infused group. The suppressed N1 amplitude of somatosensory evoked responses on the compression side, the reduced platelet aggregability, and the erythrocyte deformability by intracranial hypertension were all significantly more restored in the dextran-infused group after decompression. The percentage of platelets with volumes between 21.75 and 48.75 cu µ (normal 9.75 to 12.75 cu µ) significantly increased after decompression. Activation of platelets during intracranial hypertension leads to an increase in platelet volume from platelet aggregation, and correlates with a decrease in platelet aggregability. It was also suggested that reduction of erythrocyte deformability was not caused by erythrocyte aggregation.

The authors emphasize the role of intravascular factors such as vascular obstruction by platelet aggregates, and difficulty in passage of erythrocytes through capillaries due to reduced deformability, in the disturbance of the microcirculation following acute intracranial hypertension. The protective effect of dextran 75 by inhibition of platelets as well as hemodilution is stressed.

KEY WORDS · intracranial hypertension · intravascular aggregation · platelet aggregability · erythrocyte deformability · dextran 75 · hemodilution

RECENTLY, it has been suggested that intravascular factors may play an important role in the disturbance of the microcirculation. Hekmatpanah22,23 has reported that reduction and cessation of the circulation during and after intracranial hypertension produced by placement of an epidural balloon was caused not only by external compression of the vessels, but also by internal occlusion with sludged cells, microemboli, and intravascular clotting in the capillaries and small vessels. Kim and Sano25 have reported that activation of platelets as well as morphological changes of platelets and erythrocytes may contribute to the occurrence of a no-reflow phenomenon following cerebral ischemia induced by both raised cisterna magna pressure and lowered blood pressure. Furthermore, Mead, et al.,30 reported that reestablishment of circulation by isovolemic hemodilution with 6% dextran in isotonic saline (dextran 75) reduced mortality from 95% to 50% following compressive intracranial injury in dogs. These results indicate that the initial damage is vascular rather than injury to the parenchyma.

We studied the role of intravascular factors in the disturbance of the microcirculation following intracranial hypertension, and the effect of isovolemic hemodilution with dextran 75* on intravascular factors, cerebral perfusion, and evoked responses after relief of intracranial hypertension.

* 6% Gentran 75 (dextran 75) in 0.9% sodium chloride injection manufactured by Travenol Laboratories, Inc., Deerfield, Illinois.
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Materials and Methods

Thirty-two unselected cats, weighing from 3.0 to 4.5 kg, were anesthetized with ketamine hydrochloride (30 mg), intubated, immobilized with tubocurarine chloride (1.5 mg), and ventilated with room air using a respirator adjusted to maintain arterial Pco2 between 30 and 40 mm Hg. Acute intracranial hypertension was produced by inflation of an epidural balloon inserted into the right middle fossa through a small burr hole. Physiological saline (0.2 ml) was infused into the balloon every 10 minutes until the somatosensory evoked responses became flat bilaterally. The balloon was deflated 10 minutes later.

Animals were divided into four groups. Group 1 was the control group of 10 animals. After intracranial hypertension, the balloon was deflated and animals were observed for 4 hours without infusion of dextran 75. At 15 minutes and 4 hours after balloon deflation, platelet aggregability (PA) in response to adenosine diphosphate (ADP), volume distribution of platelets, platelet counts, erythrocyte deformability, erythrocyte volume, and hematocrit were measured. Somatosensory evoked responses (SER) and auditory brain-stem evoked responses (BER) were recorded at each increment of saline, and at 1/4, 1, 2, 3, and 4 hours after balloon deflation. Four hours after deflation of the balloon, a polyethylene catheter was inserted into the aortic arch through the femoral artery to perfuse the brain with a solution of 15 ml of India ink mixed with 15 ml of 10% formalin. The perfusate exited via the severed external jugular vein. Saturated KCl (5 ml) was also injected through the femoral vein to sacrifice the cats midway through the perfusion. Brains were removed, fixed in 10% Formalin, and studied for cerebral perfusion.

Group 2 contained nine animals. The only difference from Group 1 was isovolemic hemodilution with dextran 75 immediately after sampling the blood for hematological examinations, 15 minutes after balloon deflation. We used isovolemic hemodilution to avoid an increase in intracranial pressure caused by an increase in the circulating blood volume. Using a catheter inserted into the femoral vein, 10 ml of blood was drawn and 10 ml of dextran 75 was infused. The same procedure was repeated four times and, in total, 40 ml of dextran 75 and blood was exchanged.

Group 3 contained five animals and Group 4 eight. These cats were prepared for basic study of the effect of hemodilution on hematological parameters without intracranial hypertension. In Group 3, isovolemic hemodilution with 40 ml of dextran 75 was performed, and PA, platelet count, and erythrocyte volume were measured before and 3.75 hours after dextran infusion (this is equivalent to 4 hours after decompression in Group 2). In Group 4, the same amount of blood and dextran 75 in four cats, or physiological saline in four, were exchanged until the animals died, and correlation between hematocrit and erythrocyte deformability was studied.

Platelet aggregability was measured by the optical density method. Blood was drawn from the femoral vein before compression, and from the right external jugular vein after decompression, in a plastic syringe with a No. 22 needle. We mixed 3.6 ml of blood with 0.4 ml of 3.8% trisodium citrate dehydrate. The platelet-rich plasma (PRP) was prepared by centrifugation at 800 rpm for 7 minutes and incubated at room temperature. The platelet-poor plasma (PPP) was prepared by centrifuging PRP at 4000 rpm for 10 minutes. The aggregation curve was recorded with an aggregometer for 4 minutes after adding ADP diluted in distilled water to bring the final concentration in the aggregometer cuvette to 20 μm. The percent aggregation was calculated using the method described by Weiss and Rogers:

\[
\% \text{aggregation} = \frac{OD_{\text{initial}} - OD_{\text{maximum}}}{OD_{\text{initial}}} \times 100,
\]

where OD = optical density.

For measurement of platelet volume, 2 ml of blood from the right external jugular vein was placed in a 2-ml tube containing 0.05 ml of 7.5% liquid ethylenediaminetetraacetate (EDTA). The volume of platelets was measured by a Coulter Counter ZBI with a Coulter Channelizer II. A preparation of 6.6 μl of PRP diluted with 20 ml of Isoton II in an Accuvette II was drawn through the 100-μ aperture of the Coulter Counter, and the number of platelets at 100 different sizes from 3.75 to 78.00 μ was counted and recorded by an X-Y recorder. The percentage was calculated for every four different sizes. The platelet count was measured by a Toa platelet Counter PL-100.

Erythrocyte deformability was determined by a filtration method developed by Reid, et al. For this measurement, 2 ml of blood from the right external jugular vein was anticoagulated with EDTA, and filtered through a polycarbonated membrane with 5-μm diameter pores, then fixed in a membrane holder at a pressure gradient of 20 cm of water. The deformability index (DI) was recorded as the blood volume (ml) passing through the membrane filter in 1 minute.

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‡ Platelet Aggregation Profiler (PAP 2A) manufactured by BIO/DATA, Willow Grove, Pennsylvania.

§ Coulter Counter ZBI and Coulter Channelizer II manufactured by Coulter Electronics, Inc., Hialeah, Florida.

|| Isoton II and Accuvette II manufactured by Curtin Matheson Scientific, Inc., Houston, Texas.

* X-Y recorder II manufactured by Coulter Electronics, Inc., Hialeah, Florida.

† Toa Platelet Counter PL-100 manufactured by Toa Medical Electronics Co., Ltd., Kobe, Japan.

‡‡ Nucleopore membrane N500 CRP 013 00 and nuclear membrane holder FH 013 0010 manufactured by General Electric Co., Pleasantown, California.
Blood for erythrocyte volume was sampled in the same manner as for platelet volume. A solution of 1.0 cu μ of whole blood diluted with 30 ml of Isoton II, and a 100-μ aperture tube were used. The Coulter Counter and Channelizer were adjusted for a volume range from 13.0 to 273.0 cu μ.

The SER evoked by bilateral ulnar nerve stimulation (0.5 Hz frequency, 30 V intensity, and 0.2 msec duration) were recorded from bilateral needle electrodes inserted through the scalp to the skull over the primary somatosensory areas. The BER evoked by 70 dB click stimulation were monitored from a needle electrode placed on the skull at the vertex.

Results

Perfusion and Morphology

In the control group, intracerebral hematomas in the temporal lobe occurred in two cats, and secondary brain-stem hemorrhages and petechiae were found in two and eight cats, respectively, out of 10 cats. Of the nine dextran-infused animals, intracerebral hematomas in the temporal or parietal lobes were demonstrated in two, secondary brain-stem hemorrhages in two, and petechiae in seven. The incidence of these morphological changes was almost the same in the two groups.

Impaired perfusion was demonstrated in three cats (30%) in the control group, and in one cat (11%) in the dextran-infused group. Impaired perfusion occurred in the right temporal lobe, left thalamus and parasagittal cortex, and rostral brain stem. There was a tendency for impaired perfusion to occur in the cats with intracerebral hemorrhage in the control group.

Evoked Responses

Changes in the amplitude of SER and BER in the control group are shown in Fig. 1 with dotted lines. An analysis of variance (ANOVA) and Dunnett's test showed that the N1 peak of the right-sided SER was significantly reduced (F(10, 165) = 17.4, p < 0.01) from the precompression responses at balloon volumes greater than 0.8 ml. Waves V and IV of the BER were significantly suppressed at balloon volumes greater than 1.0 and 1.4 ml (F(12, 148) = 6.3, p < 0.01, and F(14, 202) = 7.1, p < 0.01), respectively. The N1 peak of the left-sided SER was significantly suppressed (F(12, 195) = 10.3, p < 0.01) when the balloon volume exceeded 2.0 ml. Meanwhile, Waves I, II, and III of the BER did not show significant reduction during compression and after decompression. As described above, amplitude of the right SER was suppressed first, followed by Waves V and IV of the BER, then the left SER at the terminal stage. After deflation of the balloon, recovery of the right SER was poor, and the mean amplitude at 4 hours after decompression was only 5.1% of that before compression. The left SER and Waves V and IV of the BER were restored after deflation, and the mean amplitude was 62.5%, 58.1%, and 60.3% of that before compression, respectively, at 4 hours after decompression.
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Platelet Aggregability

The mean percent aggregation of platelets (PA) in the 10 control animals was 69.7 ± 9.5% (mean ± SD) in the femoral vein before compression, and 53.1 ± 18.0% in the femoral vein and 34.4 ± 10.9% in the jugular vein 15 minutes after decompression. Four hours after decompression, values were 47.6 ± 29.1% in the femoral vein and 33.8 ± 27.8% in the jugular vein. A two-way ANOVA, Dunnett's, and paired t-test showed that the PA was significantly reduced from before compression at 15 minutes, and at 4 hours after decompression in both the femoral and jugular veins (F(2,22) = 12.2, p < 0.01). A paired t-test also demonstrated that the PA of the jugular vein sample was significantly reduced as compared with that from the femoral vein 15 minutes after decompression (t = 5.3, p < 0.05) (Fig. 2 left). Figure 2 right shows individual values of the PA in the jugular vein samples. Eight cats had complete measurements throughout the experiment: five perfused well and three poorly. The mean PA of good and impaired perfusion groups was, respectively, 66.1 ± 10.4% and 73.1 ± 9.1% before compression, 33.7 ± 22.0% and 25.2 ± 8.9% at 15 minutes after decompression, and 46.1 ± 29.0% and 13.3 ± 4.9% at 4 hours after decompression. An independent t-test showed that the PA of the impaired perfusion group was significantly lower than that of the good perfusion group 4 hours after decompression (t = 3.0, p < 0.05) (Fig. 2 right).

The mean PA in the dextran-infused group was compared with that of the control group in Fig. 3. The

Hematological Parameters

Platelet Aggregability. The mean percent aggregation of platelets (PA) in the 10 control animals was 69.7 ± 9.5% (mean ± SD) in the femoral vein before compression, and 53.1 ± 18.0% in the femoral vein and 34.4 ± 10.9% in the jugular vein 15 minutes after decompression. Four hours after decompression, values were 47.6 ± 29.1% in the femoral vein and 33.8 ± 27.8% in the jugular vein. A two-way ANOVA, Dunnett's, and paired t-test showed that the PA was significantly reduced from before compression at 15 minutes, and at 4 hours after decompression in both the femoral and jugular veins (F(2,22) = 12.2, p < 0.01). A paired t-test also demonstrated that the PA of the jugular vein sample was significantly reduced as compared with that from the femoral vein 15 minutes after decompression (t = 5.3, p < 0.05) (Fig. 2 left). Figure 2 right shows individual values of the PA in the jugular vein samples. Eight cats had complete measurements throughout the experiment: five perfused well and three poorly. The mean PA of good and impaired perfusion groups was, respectively, 66.1 ± 10.4% and 73.1 ± 9.1% before compression, 33.7 ± 22.0% and 25.2 ± 8.9% at 15 minutes after decompression, and 46.1 ± 29.0% and 13.3 ± 4.9% at 4 hours after decompression. An independent t-test showed that the PA of the impaired perfusion group was significantly lower than that of the good perfusion group 4 hours after decompression (t = 3.0, p < 0.05) (Fig. 2 right).

The mean PA in the dextran-infused group was compared with that of the control group in Fig. 3. The

Fig. 2. Left: Alterations of the mean platelet aggregability (PA) in response to adenosine diphosphate in the control group. The PA was significantly reduced at 15 minutes and 4 hours after decompression compared to before compression in both the femoral (dashed line) and the right external jugular (solid line) veins (single asterisks, p < 0.05). The PA in the right external jugular vein was more reduced than that in the femoral vein at 15 minutes after decompression (double asterisks, p < 0.05). Right: Alterations of the PA in the good and impaired perfusion animals in the control group. The PA was completely measured throughout the experiment in eight of 10 cats. In these eight cats, the PA in the impaired perfusion group was more reduced than that in the good perfusion group (asterisk, p < 0.05). Solid and dashed lines refer to the impaired and good perfusion groups. Fine and thick lines show the individual and the mean values, respectively. The mean values are from eight cats with complete measurements.

Fig. 3. Alterations in the mean platelet aggregability (PA) to adenosine diphosphate in the control (dashed line) and dextran-infused (solid line) animals. The PA was significantly reduced from precompression values in both groups at 15 minutes after decompression, and in the control group at 4 hours after decompression (single asterisk, p < 0.01). The PA was significantly better restored in the dextran-infused group compared to the control group at 4 hours after decompression (double asterisk, p < 0.01).
Fig. 4. Left: Alterations in the distribution of platelet volume in the control group. The peak volume of platelets ranged from 9.75 to 12.75 cu μ (V = 3). At 15 minutes and 4 hours after decompression, percentage of platelets with volumes between 21.75 and 51.75 cu μ (V = 7 – 16) increased from the control (asterisks, p < 0.05). Each number (V) of the abscissa shows the platelet volume between 3V + 0.75 and 3V + 3.75 cu μ. Right: Alterations in the distribution of platelet volume in the dextran-infused group. The percentage of platelets with volumes of 18.74 to 48.75 cu μ (V = 6 – 15) significantly increased at 15 minutes after decompression (asterisks, p < 0.01). The distribution returned almost to precompression levels at 4 hours after decompression. Each number (V) of the abscissa shows the platelet volume between 3V + 0.75 and 3V + 3.75 cu μ.

Platelet Volume. The mean distribution of platelets in the control group before compression, and at 15 minutes and 4 hours after decompression in six animals, and results of a two-way ANOVA, Dunnett’s, and Scheffé’s tests are demonstrated in Fig. 4 left. The peak volume of platelets ranged from 9.75 to 12.75 cu μ (V = 3, see Fig. 4). At both 15 minutes and 4 hours after decompression, the percentage of platelets with volumes smaller than 15.75 cu μ (V = 1 – 4) decreased (p < 0.01 or 0.05). On the other hand, the percentage of platelets with volumes between 21.75 to 51.75 cu μ (V = 7 – 16) increased from controls. There was no significant difference in volume distribution between 15 minutes and 4 hours after decompression.

In the dextran-infused group, although the percentage of platelets with volumes between 18.75 and 48.75 cu μ (V = 6 – 15) also significantly increased similar to the control group (F(48,336) = 8.1, p < 0.01), there was no significant difference between the values obtained before compression and those obtained 4 hours after decompression (Fig. 4 right).

Platelet Count. The mean platelet counts in eight control animals were (340.9 ± 99.0) x 10^3/cu mm before compression, (325.2 ± 64.8) x 10^3/cu mm at 15 minutes after decompression, and (312.4 ± 65.0) x 10^3/cu mm at 4 hours after decompression. A one-way ANOVA showed no significant difference between them. The mean platelet count in nine dextran-infused animals was (429.1 ± 190.7) x 10^3/cu mm before compression, and was significantly reduced to (238.8 ± 110.8) x 10^3/cu mm at 4 hours after decompression as determined by a paired t-test (t = 4.1, p < 0.001).
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A one-way ANOVA showed no significant difference among them. The mean hematocrit in nine dextran-infused animals was 41.4 ± 6.0% before compression, and was significantly reduced to 25.7 ± 41.7% (as determined by a paired t-test; t = 6.8, p < 0.001) at 4 hours after decompression.

In Group 3 (dextran infusion without intracranial hypertension), PA, platelet volume, and erythrocyte volume did not show significant change in the values before and 3.75 hours after dextran 75 infusion. In Group 4 (dextran or saline infusion without intracranial hypertension), the DI of erythrocytes gradually increased between 26% and 22%, and markedly increased below 22% hematocrit. Since there was no significant difference between dextran- and saline-infused groups, it is likely that an increase in the DI was caused by a reduction of hematocrit associated with hemodilution (Fig. 5 right).

Discussion

Intravascular Factors in Impaired Microcirculation

Platelets. Our study showed that platelet aggregability (PA) was reduced without a significant decrease in platelet count following intracranial hypertension. Furthermore, PA was more reduced in the external jugular vein than in the femoral vein 15 minutes after decompression. These results suggest that the reduction of PA was caused not by a reduction in the platelet count, but by altered function of platelets as a consequence of intracranial stress. The percentage of platelets with a volume from 21.75 to 51.75 cuμ increased. It seems that the increase of large platelets is correlated with the increment of platelet aggregates caused by activation of platelets.

A reduction in platelet aggregability has been reported in the acute stage of intracerebral and subarachnoid hemorrhage, and in sickle-cell disease. Barnhart, et al., and Gilroy, et al., have reported that platelets were significantly activated in acute stroke as compared to the normal distribution. An increase of platelet aggregates has also been shown in vaso-occlusive crisis of sickle-cell disease, in transient ischemic attacks, and in experimental cerebral ischemia.

Although the precise mechanisms involved in reduced PA are not known, previous investigators have suggested that activation of platelets in the vascular space could make platelets refractory to aggregating agents in vitro. In our compressive intracranial hypertension, both mechanical compression and ischemia can damage the vascular endothelium. On contact with damaged vascular endothelium, platelets will release thromboxane A₂ (TXA₂). Moreover, ischemic cerebral tissue can release catecholamine, arachidonic acid, TXA₂, or ADP, all of which activate platelets. It has been shown that injection of ADP, catecholamine, or arachidonic acid into normal vessels can produce obstructive platelet aggregates in vivo. Although it was not significant, the

Erythrocyte Deformability. The deformability index (DI) of erythrocytes in eight control animals was 0.84 ± 0.23 before compression, 0.60 ± 0.33 at 15 minutes after decompression, and 0.55 ± 0.28 at 4 hours after decompression. A repetitive one-way ANOVA and Scheffe's test showed that the DI at 15 minutes and 4 hours after decompression was significantly reduced from controls (F(2,14) = 20.8, p < 0.01) (Fig. 5 left).

The DI of erythrocytes in eight dextran-infused animals was 0.87 ± 0.33 before compression, 0.47 ± 0.32 at 15 minutes after decompression, and 1.12 ± 0.48 at 4 hours after decompression, respectively (Fig. 5 left). A two-way ANOVA showed that the DI in both groups was significantly reduced at 15 minutes after decompression, and in the control group at 4 hours after decompression (F(2,14) = 20.8, p < 0.01). An independent t-test showed that the DI in the dextran-infused group was significantly higher than in the control group at 4 hours after decompression (t = 2.3, p < 0.05).

Erythrocyte Volume. The peak volume of erythrocytes ranged from 44.2 to 55.2 cuμ in the control and dextran-infused groups. Throughout the experiment, there was no significant change in volume distribution in either group.

Hematocrit. The mean values of the hematocrit in eight control animals were 36.9 ± 3.1% before compression, 34.4 ± 3.8% at 15 minutes after decompression, and 33.2 ± 3.9% at 4 hours after decompression.

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reduction in platelet count after decompression may be caused by the consumption of platelets for production of aggregates. The aggregates thus formed may occlude the vessels and contribute to the propagation of ischemic brain damage. Thus, all the sequelae of intracranial hypertension may participate in an increase of platelet aggregates and reduction of platelet aggregability.

**Erythrocytes.** The erythrocyte deformability is important as a factor influencing flow within the microcirculation. The erythrocyte deformability may be defined as those geometric and physical characteristics that permit a cell whose greatest diameter normally exceeds 8 μ to pass through capillaries which range from 3 to 12 μ in diameter.41

According to Weed, the remarkable deformability of a normal mature erythrocyte appears to rely on at least three key factors: 1) Maintenance of the bi-concave shape which in turn depends on a high ratio of surface area to volume. Decrease in the ratio of surface area to volume (shape transformation from normal bi-concave to crenated or spherical red cells) will result in the ability of the cells to negotiate restricted passages within the microcirculation. 2) Normal internal fluidity of the cells, which depends primarily on the properties of normal hemoglobin. 3) Intrinsic membrane deformability which is significantly affected by the relationship between intracellular ATP, calcium, and magnesium, and may be affected by pH and oxygen tension in local regions.

A reduction of the erythrocyte deformability has been reported in patients who have vascular disease. Kim and Sano have reported that deformed erythrocytes appeared in cerebral ischemia induced by raised cisterna magna pressure and hypotension. It has also been said that the erythrocyte deforms when it encounters damaged vascular endothelium.

In our experiment, the erythrocyte deformability markedly decreased without any change in erythrocyte volume, following intracranial hypertension. Since it is unlikely that hemoglobin solubility changed throughout the experiment, this reduction of the deformability index could be best explained by shape transformation or membrane damage of erythrocytes.

In compressive intracranial hypertension, both previously reported mechanisms (namely ischemic and vascular endothelial damage caused by mechanical distortion, and fibrin deposits associated with intravascular platelet aggregation) can participate in the transformation of erythrocyte shape. Besides that, decreased pH and reduced oxygen tension during increased intracranial pressure may also induce membrane damage of erythrocytes. Our results suggest the possibility of microcirculatory disturbance after decompression, caused in part by difficulty in erythrocyte passage through capillaries due to reduction of deformability.

**Impaired Perfusion.** These results suggested that impaired perfusion was caused by intravascular factors such as abnormalities of platelets and erythrocytes. As previously discussed, vascular obstruction by platelet aggregates and shape transformation of erythrocytes may contribute to the disturbance of the microcirculation. On the other hand, all the cats in the impaired group had intracerebral hemorrhage which may be one of the causes of impaired perfusion in these animals. However, we wish to stress that the more severe vascular damage caused by hemorrhage plays an important role in activation of platelets and transformation of erythrocyte shape, which precedes obstructive platelet aggregates and reduction of the erythrocyte deformability, thus compromising the microcirculation.

**Protective Effect of Dextran 75 on Impaired Microcirculation**

The appearance of macroscopically impaired cerebral perfusion 4 hours after decompression was reduced from 30% in the control group to 11% in the dextran-infused group. The N1 amplitude of SER on the compressed side was significantly more restored in the dextran-infused group than in the control group at 2, 3, and 4 hours after balloon deflation. There was no significant difference between the two groups in evoked responses during balloon inflation, in hematological parameters before compression and 15 minutes after decompression, and in morphological changes 4 hours after decompression. These data suggest that the improvement in the dextran-infused group is not attributable to differences in the degree of brain damage between the two groups, but to the beneficial effect of isovolemic hemodilution with dextran 75.

Dextran has the following three beneficial effects: 1) a hemodiluting effect; 2) an antithrombotic effect; and 3) disaggregation of previously aggregated blood cell structures. With its hemodiluting effect, dextran has been reported to decrease the blood viscosity and the peripheral vascular resistance, and increase cerebral blood flow.

With respect to the antithrombotic effect of dextran, various forms of suppressive effects on platelet function, such as platelet aggregation, and ADP release from platelets, have been reported. These are thought to be caused by the inhibition of platelet Factor III and Factor VIII activity, and surface coating of the platelets. In the dextran-infused group, reduced PA increased the percentage of larger platelets 15 minutes after decompression beyond those levels obtained in the control group 4 hours after decompression. Gilroy, et al., have reported restoration of activated platelets toward normal; that is, the number of platelet aggregates and platelets with activated forms declined, and the number of platelets with inactivated forms increased after dextran infusion in acute stroke patients. It is, therefore, possible to assume that a
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decrease in the percentage of platelets with larger volumes reflects a decrease in the number of platelet aggregates, and a restoration of the PA was a result of form changes of platelets from the activated to the inactivated state.

As to the effect of dextran on erythrocytes, it has been reported that dextran 40 disaggregates the aggregated blood cells by changing the red cell surface charge, and improves the capillary flow and increases peripheral circulation. In the dextran-infused group, the reduced DI of erythrocytes (0.47) at 15 minutes after decompression was restored to 1.12 at 4 hours after decompression. This appears to be caused by a direct effect of dextran on the erythrocytes. As shown in Fig. 5 right, however, a comparison between the hematocrit and erythrocyte deformability in the dextran- and saline-infused groups showed no marked difference in the two groups. Although we cannot be sure about the direct effect of dextran on erythrocyte deformability, this result suggests that the restoration of erythrocyte deformability may be mainly caused by a reduction of hematocrit associated with hemodilution.

Our result shows that postcompressive neuronal dysfunction is, at least in part, due to impaired perfusion and can be ameliorated by improving blood flow. Dextran can decrease the blood viscosity and peripheral vascular resistance by hemodilution and may transform the activated platelets to the inactivated form by its antithrombotic effect. Thus, dextran can restore the impaired microcirculation, and improve the neuronal dysfunction.

Our finding that dextran 75 restored impaired microcirculation and improved neuronal dysfunction does not necessarily mean that dextran 75 is a useful drug in head-trauma patients, but only stresses the existence of microcirculatory disturbance after intracranial hypertension caused by intravascular factors. We used dextran 75 because of its antithrombotic effect, and its demonstrated beneficial effect on activated platelets. For clinical use, however, isovolemic hemodilution with dextran 75 has serious drawbacks, namely, 1) cerebral hypoxia caused by anemia and blockage of the microvasculature with intravascular erythrocyte aggregation, and 2) prolongation of the bleeding time. Since it is possible that brain tissue damaged by intracranial hypertension is more vulnerable to hypoxia, isovolemic hemodilution with dextran 75 would require extensive oxygen therapy. Furthermore, in head-trauma patients who have cerebral contusion, prolongation of bleeding time induced by infusion of dextran 75 may predispose to intracerebral hemorrhage.

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