Experimental In Vivo Microcirculatory Dynamics in Brain Trauma

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TRAUMA to the central nervous system has long been one of the major problems encountered in the practice of neurosurgery in both the military and the civilian environments. Massive open or penetrating wounds to the central nervous system, while posing great problems in clinical management, entail a rather well-defined pathophysiological problem. However, closed head trauma with concussion, direct damage, contre-coup injuries, and compromise of major vessels and laceration. But many excellent studies have established beyond doubt that microscopic degenerative changes can occur in trauma without gross or microscopic evidence of tissue disruption.

The first description of petechial perivascular hemorrhages and diffuse cerebral swelling secondary to closed head trauma, without focal damage, is a part of the oldest medical records. In 1831, Bright’s excellent studies documented this finding in postmortem material from clinical and laboratory sources. Photomicrographs have revealed microscopic distention and leakage of vessels at the capillary level with resultant, microhemorrhagic changes.

Recently we have seen several patients who died secondary to closed head injuries but in whom no gross contusions, laceration, or bleeding was noted. Diffuse cerebral edema was present as well as microscopic foci of perivascular hemorrhages. In an effort to clarify the underlying pathophysiology of such changes, we have undertaken the present study. Although postmortem changes have been widely documented, there has been no previous report of the in vivo microcirculatory dynamics that occur following brain trauma.

Materials and Methods

Ten animals comprised the experimental series for this study, consisting of 4 mongrel dogs, 3 Rhesus monkeys (Macacus mulata), and 3 baboons (Papio porcarius). All animals were subjected to identical operative procedures. They were anesthetized by intravenous pentobarbital in a dosage of 30 mg/kg of body weight. The baboons required the pre-anesthetic administration of 40 mg of phencyclidine hydrochloride to make safe removal from their cages possible. After induction of anesthesia, a slow intravenous infusion was continued in order to maintain a route should further anesthesia be required. The airway was maintained by endotracheal intubation. The Harvard pump respirator was available should ventilatory assistance be required, but this was seldom used.

The head was closely clipped and immobilized in a stereotaxic ear press head holder to eliminate any possible movement. The operative site was prepared with a thimerosal solution and appropriately draped. The scalp was opened in a midline linear incision extending from the glabella to the inion by the cutting current of the Bovie electrocautery unit, which minimized scalp blood loss. The temporalis muscles were detached by incising the fascial and pericranial attachments along their superior margins and stripping these away from the cranial surfaces. Self-retaining retractors were used to retract the scalp.

† The principles of laboratory animal care, as promulgated by the National Society for Medical Research, were observed during this study.

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Fig. 1. Pre-trauma appearance of artery and vein over cortical gyrus. Baboon brain, ×16.

Fig. 2. Immediate post-traumatic cortical appearance that shows the perivenous flush. Baboon brain, ×40.

Fig. 3. Early petechial formation at capillary venous junctions with a persistent flush around the vein after 4 minutes. Baboon brain, ×25.

Fig. 4. Petechial formation is more advanced and the flush is less prominent after 10 minutes. Baboon brain, ×25.

Fig. 5. Petechial formation is most marked at the venous capillary junction at 20 minutes. Baboon brain, ×40.
magnification previously observed. This consisted of either a 300 or 400 gram-centimeter force delivered to an area of the gyrus that varied from 0.5 to 1.5 cm in diameter by allowing a standard cylindrical brass weight to fall vertically down a 10 or 15 cm long glass tube onto the desired surface. After the concussive force hit the cortical surface, it was closely observed over the following 3 to 4 hours, with serial photographs of the resulting changes; these photographs varied in magnification from 16X to 40X, usually the latter.

All observations were made with the Zeiss operating microscope. When conditions indicated, a Leitz 642268 microscope mounted with waterproof lens and stock movie camera was also used with magnifications from 50X to 100X for cinephotography of the subject vessels.

As the area of cortex exposed was relatively large, it was possible to repeat the procedure several times on the same animal and still allow wide separation of the lesions. In this manner, on the 10 subject animals over 60 individual lesions were studied and serially photographed. The observations were made with attention centered on micro-circulation and perivascular responses.

At the conclusion of the study, the animals were sacrificed with large doses of barbiturates and the brains immediately removed for pathological analysis. The brains were suspended in 10% buffered formalin and allowed to fix. Serial coronal sections were then performed through the regions subjected to trauma. Representative areas were sectioned at 6μ, stained with hematoxylin and eosin, and studied microscopically in the standard manner.

Results

Species Variation. In this fairly wide range of animals (dog, Rhesus monkey, and baboon), there were no appreciable variations between the different species. The observed changes occurred with no measurable difference so far as time of onset, degree of involvement, or basic phases of evolution were concerned.

Normal Vessels. There was no problem in distinguishing between arterial and venous channels, due to characteristic differences in color and in configuration. The veins were, of course, of a darker hue than arteries. The arterial pattern was generally one of a long rather sinuous vessel with intermittent distinct lesser branches (Fig. 1). The pial veins, on the other hand, had the appearance of a stocky tree with its trunk based on a larger vein in an adjacent sulcus. The primary tributaries were short and stubby, ending rather abruptly in multiple tertiary branches (Fig. 1) which were about 0.05 mm in diameter and thus represented the smallest venules and capillary-venous junctions.

There were occasional direct arteriovenous communications noted through the smaller caliber venous and arterial arborizations in the size range of 0.10 to 0.20 mm.

Venous Changes Following Trauma. The earliest change which followed trauma to the cortical surface was a pronounced perivascular blush. This blush under higher magnification (Figs. 2 and 3) proved to be the result of capillary dilatation and decreased ve-
locity of blood flow in both the capillaries and smaller veins. This was not strictly confined to the traumatized point, but was never observed more than 10 mm beyond the impact area. These changes occurred within 1 minute following trauma and gradually became more pronounced until a plateau was attained at about 5 minutes; concomitant and comparable engorgement of the larger veins was also observed.

After about 5 to 6 minutes, when these changes had become quite pronounced, perivenous extravasations and petechiae began to appear. The most marked petechial changes occurred at the points of maximal deformation of the cortical surface; that is, they tended to occur more along the margin of the impact area than over its entire surface (Figs. 3 and 4). These petechiae occurred without exception at the level of the capillary-venous junction (Figs. 4 and 5), appearing as tiny bluish surface discolorations measuring usually less than 0.3 mm at the pial surface. In cut sections, however, these proved to be considerably longer, measuring sometimes as large as 2 mm in diameter (Fig. 6). Thus, extension of the perivenous hemorrhages within the cortex seemed more usual than a subpial surface spread. The perivenous petechiae were of fairly constant dimensions. In lesions of relatively greater severity, larger hemorrhagic areas occurred by coalescence of the individual hemorrhages rather than by enlargement of the individual petechiae.

Over a period of several minutes, edema and swelling of the surrounding cortex occurred, progressing some 15 minutes later to actual protrusion of the area of the lesion above the surrounding surfaces.

Segmental occlusions of certain small venous channels in the areas of contusion occurred late in the sequence of events, apparently secondary to microthrombi formation in areas of vascular sludging. These irreversible changes produced tremendously dilated short vascular segments between areas of complete occlusion, and were apparently the end result of the initial dilatation and reduction in flow velocity.

All the changes above had occurred by 45 minutes post-trauma (Fig. 7). Further observations up to 4 hours revealed no progression of these events with the exception of minimal increases in the degree of swelling.

Arterial Changes Following Trauma. Within a matter of seconds following trauma, the small arterioles were observed to manifest a transient local spasm and decreased flow. This occurred in the cortical area where no bleeding was encountered. In a few instances when the trauma resulted in some bleeding, a rather marked spastic phenomenon was noted. However, these changes in the arterial vessels were minimal when compared to the changes in the venous circulation.

When trauma resulted in arteriolar laceration, the hemorrhage would stop after 3 to 5 minutes as a result of occlusion of the lacerated segment by translucent thrombi, presumably composed of platelets. These thrombi were noted to form not only in the lacerated arteriolar segment, but also at the origin from the parent artery; in the main stream, they would repeatedly form and dislodge to become embolic particles to other more distal terminal arterioles. Several distant vessels were noted to be completely occluded by embolic particles temporarily for 10 to 15 minutes.

Relative Vascular Fragility. Prolonged operative exposure, even in spite of frequent saline irrigations, markedly increased the
susceptibility of the pial vessels to injury. The standardized application of trauma to a given operative area never produced initial vascular laceration or frank hemorrhage. After operative exposure for 30 to 45 minutes, however, some minimal free bleeding was often noted and occasional frank hemorrhage.

When vascular disruption occurred it was usually of venous rather than arterial channels. On rare occasions when arterial disruption did occur it was also accompanied by
venous hemorrhage. This, an addition to the petechial hemorrhages previously discussed, would indicate that veins were more susceptible to trauma than arteries.

**Discussion**

The presence of vascular changes in the central nervous system following trauma has long been recognized in the form of ring and ball hemorrhages.\(^3\) While the existence of such lesions is not questioned, their significance has been quite controversial.\(^4\) Various investigators have shown microscopically that definite neuronal\(^5\) and glial\(^6\) changes follow trauma, even in concussive trauma which does not produce grossly identifiable lesions. Attempts have been made to explain all nervous tissue changes on the basis of “molecular rearrangements,” or so-called *commotio cerebri*\(^28\) produced by brain vibrations within the closed skull. In addition, explanations have been advanced which advocate that brain trauma exerts its adverse effects by primary disruption of the myelin sheaths and axis cylinders.\(^29\) Schmaus,\(^30\) who observed clinical and experimental spinal cord traumatic lesions, described a lesion in the gray matter of the cord which he felt represented products of degenerated glia. The vascular changes were then thought to be secondary degenerative manifestations of this disruption.

More recently, certain investigations indicate that contusive or even concussive effects in brain trauma exert an adverse influence on the vascular stroma.\(^6,10,19,21,25,28,29,32,34,35\) The neuronal and glial degenerative changes observed later would then represent the secondary effects of vascular problems.\(^31,33,34\)

Even so, there is considerable disagreement as to the actual sequence of events leading to vascular incompetence and the resultant hemorrhage.

Ricker,\(^32\) Dietrich,\(^8\) and later Helfand\(^31\) were proponents of a theory of vasomotor mechanisms in the production of traumatic petechiae. They felt that the degree of changes seen could not be explained on the basis of vascular morphological alterations alone, however, but must in addition have some reflex physiological basis. An analogy was made to traumatic peripheral vascular lesions where an initial intense vasoconstric-

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still and cine photography of the pial vessels.\textsuperscript{16,10} These methods are especially suited to such problems as the delineation of the pathophysiology of trauma where changes evolve rapidly.

Within seconds following the application of trauma, the pial capillaries were observed to become markedly dilated, especially in the perivenous areas. This accounted for the marked flush which was observed initially in these regions under lower magnifications. The changes were always perivenous; neither the dilatation, blush, or subsequent leakage was ever observed in the region of arterio-lar-capillary junctions. The changes were not strictly confined to the area of direct trauma, but were often seen in immediately adjacent tissue. They were never, however, seen farther than 1 cm from the impact area. The agent or agents that trigger this dilatation remain speculative. Meyer\textsuperscript{26} feels that the local acidotic changes in areas of contusion, as manifested by lower pH measurements, are responsible for the dilatation. On the other hand, the acidotic changes, which do not occur for some 2 to 3 minutes after trauma, may themselves be the result of dilatation and stasis.

Concomitantly with the capillary dilatation, a marked slowing of circulation in these vessels was noted, which in many vessels eventually progressed to stasis, sludging, and complete arrest of flow. These alterations occurred rapidly so that within 6 to 7 minutes following trauma, leakage from some vessels and perivascular petechial formation were seen. By 10 minutes, the petechial changes had become quite marked. These hemorrhages were observed to form from rather diffuse leakage rather than from a single localized site of vascular injury. Another point in favor of the theory of leakage due to anoxemia secondary to stasis was the delayed nature of the diapedesis. When hemorrhage occurred as a direct result of traumatic lacerations, as was occasionally observed, this was evident immediately at the time of trauma. The cortical petechiae were not seen earlier than 5 minutes post-trauma and continued to develop from some 15 to 30 minutes. Perivascular hemorrhages of this sort undoubtedly result in the perivascular gliosis which is a recognized late pathological finding following brain trauma.\textsuperscript{23}

Edema of the surrounding tissue developed along with the evolution of stasis and petechiae. The edema appeared to be mainly a result of vascular leakage. This fluid loss as the result of capillary damage was locally quite marked and could well explain the severe edema and increased intracranial pressure often seen in widespread brain injury.

The role of arterial changes following a concussive or contusive blow was minimal when the trauma did not produce frank laceration and arterial disruption; minimal arterial spasm was noted but little else. All of the vascular dilatation, stasis, and petechial changes were perivenous and not perarterial. In trauma with laceration, however, the arterial changes were significant with thrombus formation in both the lacerated and the parent vessels, and migration of thrombi from the latter into areas of normal brain. In such a situation, the changes in the arterial side of the circulation are significant pathophysiological responses.

By observing the dynamic, microscopic, \textit{in vivo} changes following brain trauma, the means by which recognized pathological lesions are formed have been clarified. While the precise chemical changes that initiate these pathophysiological events remain obscure, there can no longer be any doubt as to the precise location of the changes, nor the stages in their evolution. These observations remain quite constant over a wide species range, and therefore it is probable that they also would be applicable to man.

\textbf{Summary}

The microvasculature of the brain surface was observed in dogs, monkeys, and baboons to delineate the precise pathophysiology of cerebral trauma. The changes were documented on film, both still and movie, and were mainly, but not entirely, related to the venous circulation. The stages in order of evolution were capillary venous dilatation and engorgement, stasis, sludging with eventual occlusion, diapedesis with petechial formation, edema, and swelling. The only arterial change noted, when lesions were not so severe as to produce laceration, was moderate localized spasm.

The phenomena observed were identical in all species studied and were felt to be applicable to man.
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