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Resuscitation from severe brain trauma

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Abstract

Severe traumatic brain injuries are extremely heterogeneous.At least seven of the secondary derangements in the brain that have been identified as occurring after most traumatic brain injuries also occur after cardiac arrest. These secondary derangements include posttraumatic brain ischemia. In addition, traumatic brain injury causes insults not present after cardiac arrest, i.e., mechanical tissue injury (including axonal injury and hemorrhages), followed by inflammation, brain swelling, and brain herniation. Brain herniation, in the absence of a mass lesion, is due to a still-to-be-clarified mix of edema and increased cerebral blood flow and blood volume. Glutamate release immediately after traumatic brain injury is proven. Late excitotoxicity needs exploration. Inflammation is a trigger for repair mechanisms.

In the 1950s and 1960s, traumatic brain injury with coma was treated empirically with prolonged moderate hypothermia and intracranial pressure monitoring and control.Moderate hypothermia (30 degrees to 32 degrees C), but not mild hypothermia, can help prevent increases in intracranial pressure. How to achieve optimized hypothermia and rewarming without delayed brain herniation remains a challenge for research. Deoxyribonucleic

- Table 1

acid (DNA) damage and triggering of programmed cell death (apoptosis) by trauma deserve exploration.

Rodent models of cortical contusion are being used effectively to clarify the molecular and cellular responses of brain tissue to trauma and to study axonal and dendritic injury.However, in order to optimize therapeutic manipulations of posttraumatic intracranial dynamics and solve the problem of brain herniation, it may be necessary to use traumatic brain injury models in large animals (e.g., the dog), with long-term intensive care. Stepwise measures to prevent lethal brain swelling after traumatic brain injury need experimental exploration, based on the multifactorial mechanisms of brain swelling. Novel treatments have so far influenced primarily healthy tissue; future explorations should benefit damaged tissue in the penumbra zones and in remote brain regions. The prehospital arena is unexplored territory for traumatic brain injury research.

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Rosomoff: This discussion session concerning accidental traumatic brain injury should be focused more on resuscitation (postinsult therapy), rather than on protection (pretreatment). The latter approach is more relevant for protecting (preserving) the brain during elective surgery. At present, after relatively disappointing experimental and clinical trials of resuscitative drug treatment potentials, resuscitative hypothermia has evolved as the most promising treatment modality for traumatic brain injury. In Dr. Safar's algorithm of cardiopulmonary-cerebral resuscitation of 1961 [1], there was an ``H'' at the end, which introduced hypothermia as a potential cerebral resuscitation treatment (i.e., postinsult therapy). Dr. Safar likes to define mild hypothermia as 34 degrees to 36 degrees C, and moderate hypothermia as 28 degrees to 32 degrees C.

Therapeutic moderate hypothermia was introduced in the 1950s to protect the brain during circulatory arrest for open-heart surgery [2]. Studies by my colleagues and me then followed, which described the effects of hypothermia on cerebral blood flow and metabolism in the normal brain [3], along with experimental studies of brain protection-preservation [4] or resuscitation [5] for focal brain ischemia (stroke), or brain contusion [6,7]. I began hypothermia research in New York in the 1950s and came to Pittsburgh in 1959. Dr. Safar came from Baltimore to Pittsburgh in 1961. With his arrival, our neurosurgical special care (recovery) room became a true critical care unit. We jointly began to apply hypothermia for protection, preservation, and resuscitation for pathologic processes of the nervous system in patients, while I also continued my laboratory research in dogs.

We used a dog model of cold injury (``contusion'') to the cortex [6,7]. The lesion looks microscopically like a hemorrhagic contusion. Using methods which at that time were still very crude, we could nevertheless get outcome data. In normothermic controls, the cortex was essentially wiped out in the ``contused'' region. Dogs that were kept at moderate hypothermia (25 degrees to 28 degrees C), during and after the cold lesion had been set, had a less severe lesion, even when evaluated 12 hrs after the injury. We measured in brain tissue the volumes of edema and blood. After ``contusion,'' cerebral water and blood content remained constant, as long as we kept the dogs hypothermic, which was for only 1 hr. Information is needed on long-term hypothermia in higher species and patients, as long-term hypothermia is difficult to carry out in rats.

The easiest end point to measure after traumatic brain injury is death. My colleagues and I developed an appropriate regression curve and found a lesion that resulted in a 50% mortality rate. We looked at delayed induction of hypothermia [7]. I speculated that: a) there would be a critical period of time after which there would be only a partial or no effect of hypothermia; and b) whatever secondary pathogenetic events began immediately after injury, we could affect this chain of events if we could intervene early and briefly. Therefore, we applied hypothermia over only 1-hr duration immediately after traumatic brain injury. When we delayed cooling to 3 hrs after injury, and kept the dog cool for 1 hr and then rewarmed it to normothermia, 100% survived. When cooling was started between 3 and 8 hrs after injury, there was a partially beneficial effect. When cooling was started 8 hrs after injury, the mortality rate was 50%, as in the normothermic controls. Current work appears to verify this finding.

Cerebrospinal fluid pressure effects do not seem to influence outcome, provided herniation is avoided. In our dog studies, cerebrospinal fluid pressure after ``contusion'' increased during normothermia, but remained low during hypothermia. With rewarming, however, cerebrospinal fluid pressure increased to the same value as in normothermic controls. There seems to be delayed injury responding to cooling. Future research is needed on the treatment of delayed brain swelling. When we followed some animals over 6 to 12 wks, we found microscopic evidence of inflammation and early exudate, as the expected reaction to the cold injury. A reparative phase, as indicated by infiltrations of chronic inflammatory cells, began in the hypothermic group long after rewarming, at approximate 1 wk, as compared with 3 wks in the normothermic group. Brief hypothermia after traumatic brain injury lessened early edema and exudation and ultimately enhanced repair.

In Pittsburgh, from 1961 to 1965, we used moderate hypothermia in patients after brain surgery or traumatic brain injury. We used slow external exposure cooling by opening the intensive care unit windows and/or using a cooling blanket. We [8] treated more than 100 patients with long-term moderate hypothermia, keeping them cold sometimes as long as 6 wks. This prolonged cooling did not seem to result in pulmonary infection, coagulation disturbances, or other complications. In a typical patient who became febrile, we found that the brain was tremendously sensitive to mild temperature changes in either direction, and that even mild hyperthermia was not desirable--in fact, in was destructive. An example was a patient who reached a rectal temperature of 40 degrees C. When we reduced rectal temperature to 35 degrees C, she woke up. After 3 days of hypothermia, we returned the rectal temperature to normal and she again became comatose. When we then again used hypothermia for a few days, she woke up. After several such happenings, hypothermia finally was reversed and she remained awake. This temporal pattern needs explanation. Some patients would eventually recover after weeks of hypothermia. It appeared that in some patients, there was a long-term benefit from very prolonged hypothermia. Differentiating the short-term from long-term benefit should be part of future research.

Explaining details on mechanisms in that era before scanning by computed tomography (CT) or magnetic resonance imaging (MRI) was not easy, since we did not know the sizes of lesions. We did everything to rule out a mass lesion, which would need operative decompression.

Dr. Safar defines ``therapeutic'' hypothermia as low temperature without shivering (which could cause damage by increased metabolic demands), with ``poikilothermia'' induced by the ischemic or traumatic insult or by drugs. To accomplish

this procedure in our patients, we used a ``lytic cocktail,'' i.e., a titrated intravenous infusion of meperidine, pentobarbital, and chlorpromazine [9]. This infusion was usually needed for 2 to 3 days to suppress risky shivering. Later, these patients' ``thermostats'' seemed to reset themselves and they adapted to the lower temperature without the need for pharmacologic sedation. The use of depressant drugs, within the first 2 to 3 days, reduced our ability to follow neurologic parameters. Most patients breathed spontaneously, with acceptable blood gas values (by the mid-1960s, blood gas values could be reliably measured). However, there would be a slow, progressive acidemia. Some patients received prolonged, controlled ventilation via cuffed tracheostomy tubes [10]. Neurologic examination was possible, as Dr. Safar used ``softening doses'' of relaxant, with minimal or no central nervous system depressant, avoiding fully paralyzing doses.

Concerning the question by Dr. Ebmeyer about the optimal duration and levels of hypothermia after brain trauma, to avoid an intracranial pressure increase to herniation during rewarming, I can only say that this is an area of research that I walked away from three decades ago. Intracranial pressure increase seems to be relatively irrelevant as long as it does not continue to escalate past a certain point, to brain herniation. Intracranial pressure increase is a secondary result of the tissue response to injury. The biochemistry underlying this increase is an important feature to study. Intracranial pressure should be used only as one of several indices. Were fluctuations between coma and wakefulness accompanied by increased and decreased intracranial pressure? I do not know, but I do not think so. When we manipulated the intracranial pressure in dogs after experimental contusion injury, the brains were histologically the same, with or without intracranial pressure control. Our animals did not show signs of herniation.

PATHOPHYSIOLOGY

Safar: My colleagues and I recently developed and used a new dog outcome model of simulated brain trauma by temporary epidural brain compression of 90 mins, under the team leadership of Dr. Pomeranz [11] and Dr. Ebmeyer ([12], A4). This model includes epidural brain compression by balloon (volume displacement, simulating an epidural hematoma), deflation of the balloon (simulating operative drainage), and intensive care life support over 4 days until outcome evaluation was performed. In the first study [11], we found that after this traumatic brain injury, moderate total body hypothermia (31 degrees C), induced during brain compression and maintained for 5 hrs, could keep intracranial pressure normal. However, intracranial pressure increased during subsequent mild hypothermia (35 degrees C). During mild hypothermia or rewarming to normothermia, the intracranial pressure sometimes increased to the same values as in normothermic controls. Herniations occurred in both groups, but much later in the hypothermia group, which also showed smaller tissue volumes with hemorrhagic necroses than the normothermic controls. After drainage of the ``epidural hematoma,'' there was a lucid period of near-complete but transient recovery, followed by brain swelling in the control group after a few hours, and in the hypothermia group after rewarming. In our second study using this model [12], we found that more prolonged moderate hypothermia (i.e., 31 degrees C over 48 hrs) kept the intracranial pressure low even for 48 hrs. Again, during rewarming, the intracranial pressure increased, as it did after shorter hypothermia. Moderate hypothermia of 48 hrs seemed to be accompanied in some dogs by pulmonary problems and coagulopathy after rewarming. The delay of intracranial hypertension by moderate hypothermia allows time for additional therapies. This dog model [11,12] seems to be, at present, the only animal model of traumatic brain injury, in a species high on the phylogenetic scale, with the ability to manipulate intracranial dynamics after injury using ``clinical'' prolonged invasive monitoring and life support. This type of study has not

been possible in rats.

Kochanek: Therapeutic hypothermia is discussed in further detail in the article, ``Resuscitative hypothermia,'' in this issue of Critical Care Medicine. Let us look at some comparisons between cardiac arrest, trauma, and stroke with normothermia (A1). Let us try to learn from each other in these areas. The classic pattern of cerebral blood flow during reperfusion from prolonged cardiac arrest (i.e., transient hyperemia followed by protracted hypoperfusion) was first documented by Dr. Safar's group in 1970 to 1971 by Lind et al. [13] and then by Snyder et al [14]. A similar pattern has been suggested to occur after traumatic brain injury, which seems to elicit a brief, transient surge of cerebral blood flow (probably shorter than after cardiac arrest) and then a protracted period of delayed hypoperfusion [15]. In comatose patients with traumatic brain injury, there seems to be a secondary, late, hyperemic phase [16], which has also been described in seemingly hopeless cases after cardiac arrest [17-19]. This phase needs clarification. In particular, clarification is needed as to whether this delayed increase in cerebral blood flow (either absolute or relative) after traumatic brain injury leads to intracranial hypertension, or whether the intracranial hypertension is primarily the result of edema or increased intracranial blood volume. When, where, and how can ischemia be differentiated from hyperemia? What is the mechanism of protracted hypoperfusion after traumatic brain injury or cardiac arrest? The role of tissue edema causing capillary compression has been argued back and forth. Tissue edema is unlikely to be the key factor after cardiac arrest or traumatic brain injury.

The efficacy of hyperventilation early after traumatic brain injury--the standard care until recently--is being questioned. After cardiac arrest, hyperventilation has also been applied, but infrequently. The delayed secondary hyperemia could be merely an epiphenomenon after very prolonged cardiac arrest, and be a marker of impending brain death. Hyperemia after traumatic brain injury seems to be complex and may be associated with either favorable or poor outcome.

Concerning hyperosmotic agents and their effect on regional and global cerebral blood flow after traumatic brain injury, these agents currently have a role in the management of intracranial hypertension. However, future studies should be directed at understanding and targeting the injured areas of the brain, not manipulating water content in the remainder of the brain.

After traumatic brain injury, there may be hyperemia in regions with or without intact autoregulation or CO_2 reactivity. After cardiac arrest in adults, the very delayed, secondary hyperemia seems to be accompanied by a loss of CO_2 responsiveness and autoregulation, all poor prognostic signs [19].

Concerning the mechanism of late hyperemia after traumatic brain injury, our group under Dr. Clark (A2) studied immature rats, since children respond with more hyperemia than adults. We exposed the rats to a reproducible, weight-drop, cortical contusion insult. Inducible nitric oxide synthase, an enzyme that produces the endogenous vasodilator, nitric oxide, was demonstrated by immunofluorescence. Inducible nitric oxide synthase expression appeared in neutrophils and vascular smooth muscle at 24 hrs. There was no inducible nitric oxide synthase expression in nontraumatized sham experiments. This study (A2) supports the hypothesis that inflammation-derived nitric oxide contributes to posttraumatic hyperemia. We have also recently reported increased levels of adenosine, another putative vasodilator, after brain contusion. Further studies are needed to define the mechanisms involved in delayed hyperemia.

Although therapeutic hypothermia is the subject of a subsequent article (``Resuscitative hypothermia'') in this issue of Critical

Care Medicine, studies have showed that moderate hypothermia after traumatic brain injury in rats improved not only functional outcome [20], but also reduced the mortality rate (A3). In addition, moderate hypothermia reduced intracranial pressure and lesion size and delayed brain herniation in our dog outcome model of epidural brain compression [11,12].

Safar: Recent research has begun to clarify the specific derangements in brain tissue, at the cellular and molecular levels, in the response to traumatic brain injury, along with the effect of the extracerebral derangements on the injured brain (A5). After traumatic brain injury, variable combinations of multiple derangements lead to either loss of neurons and survival with permanent crippling of the person or to diffuse brain swelling, herniation, intractable apnea and hypotension, and death. Diffuse brain swelling may be compared with extracerebral tissues swelling after mechanical trauma. In posttraumatic brain swelling, beyond the mass lesions of hematomas, the relative roles of edema and hyperemia should be clarified. Optimal salvage might be accomplished by mechanism-specific combination treatments to prevent or mitigate brain swelling and thereby prevent herniation and brain death (A8).

The derangements documented or postulated to occur during and after cardiac arrest (temporary complete global brain ischemia) [21,22] also seem to occur after severe traumatic brain injury. However, severe traumatic brain injury adds several derangements not present after cardiac arrest, namely, mechanical tissue destruction (including diffuse axonal injury), hemorrhages (even space-occupying hematomas), the neurotoxic effect of heme, an inflammatory response, and an intracranial pressure increase possibly leading to herniation Table 1 (A5). Inflammatory cascades have been documented after traumatic brain injury, but these cascades have been insufficiently studied to be ruled in or out after cardiac arrest. The most important differences between the two types of insults (i.e., traumatic brain injury and cardiac arrest) are derived from the fact that in contrast to the temporary global ischemia of cardiac arrest, the following situations occur: a) traumatic brain injuries encompass a large variety of multifocal injuries; b) contused hemorrhagic foci are surrounded by potentially treatable trouble zones (penumbras); and c) initial posttraumatic brain injury (partial) functional recovery can be followed by delayed diffuse brain swelling, coma, herniation, and death. Inflammatory hyperemia and edema have been documented after traumatic brain injury (sometimes causing a lethal intracranial pressure increase), but not after cardiac arrest of 10 to 20 mins of no-flow.

Table 1. Cerebral postresuscitation syndrome: Secondary derangements after traumatic brain injury (TBI) (inhomogeneous insult, multifocal) vs. cardiac arrest (CA) (homogeneous insult, global) (by P. Safar and P. Kochanek)

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Traumatic brain injury and cardiac arrest seem to have in common the postinsult pattern of cerebral perfusion failure. For reperfusion from normothermic cardiac arrest (no-flow) of 10 to 12 mins, we have to differentiate between the so-called immediate no-reflow phenomenon [23] and, after brief hyperemia, the delayed protracted cerebral hypoperfusion [13,14]. We have been able to show in dogs after cardiac arrest, using the stable xenon computed tomography method [24-27], that the multifocal no-reflow is an issue only with hypotensive reperfusion and is ``washed away'' by diffuse homogeneous hyperemia with normotensive or hypertensive reperfusion. We also found that the protracted cerebral hypoperfusion can last from about 1 hr to about 12 hrs after reperfusion, is inhomogeneous [24,25], and can be corrected with hypertension, hemodilution, and vasodilation [26]. This low cerebral blood flow is mismatched to normal or supranormal global cerebral oxygen uptake, resulting in dangerously low cerebral venous oxygen values [13,14,25-29]. As after traumatic brain injury [16], the very delayed, secondary cerebral hyperemia after cardiac arrest seems to be a poor prognostic indicator [17-19]. After traumatic brain injury, the initial hyperemia seems to be very brief, if it occurs at all. The subsequent hypoperfusion seems to be prolonged. What remains to be studied for both insults includes the exact multifactorial pathogenesis of the hypoperfusion and the delayed secondary hyperemia, particularly as a factor in posttraumatic diffuse brain swelling.

Experimental traumatic brain injury research should not limit itself to the molecular and cellular responses to mechanical injury of brain tissue in the penumbra zone of a cortical contusion, such as is being explored in rat models, but should also consider the overall intracranial dynamics of lethal brain swelling. Studies of these overall intracranial dynamics require use of traumatic brain injury-intensive care outcome models in a species of large animals (e.g., dog, cat, pig, or monkey) (A4). One must be able to compare standard with experimental life-support methods, comparing their effects on intracranial dynamics and correlating these effects with clinical (functional) and morphologic outcome; long-term outcome is the most meaningful end point [11,12]. The great differences in the pathophysiology and therapeutic potentials between different types of brain trauma (e.g., blunt, acceleration, penetrating, compression by hematoma) make relevant animal modeling difficult. Moreover, the limits of tolerance by the normal brain to hypotension, hypoxemia, temperature extremes, osmotic changes, and other derangements differ considerably from those limits tolerated by the injured brain. For example, the normal brain can tolerate high fever, while the injured brain cannot even tolerate minimal hyperthermia. Some derangements, such as the inflammatory response, develop slowly after traumatic brain injury, which gives therapeutic trials more time than after cardiac arrest (A8).

White: There are excellent studies in human trauma patients by Marion et al. [30], where cerebral blood flow measurements were made rather early after traumatic brain injury. These studies showed cerebral blood flow values of less than 20 mL/100 g/min (approximate 40% of normal), at least in some brain regions, while there were other regions with normal cerebral blood flow. One of the clinical questions to be clarified is whether or not hyperventilation is appropriate after traumatic brain injury. I am not sure whether the ``Robin Hood phenomenon'' occurs, i.e., increasing cerebral blood flow in abnormal regions through hyperventilation-induced vasoconstriction in responsive normal regions. At 1 to 2 hrs after traumatic brain injury, one can find an intracranial pressure increase when the CT image shows hemorrhage. There is a great difference between cardiac arrest and trauma as it concerns the actual primary physical injury causing tissue destruction.

Grenvik: My colleagues and I [31] performed a preliminary positron emission tomography study on patients in persistent

vegetative states after cardiac arrest and cardiopulmonary resuscitation with restoration of spontaneous circulation. Cerebral blood flow did not correlate with outcome, but oxygen uptake of the brain seemed to do so. When initially low cerebral oxygen uptake continued to decrease, even when cerebral blood flow increased, outcome was poor. When oxygen uptake increased, it was a good sign. Late hyperemia may be due to vasodilation as a result of secondary metabolites and cytokines. I agree with Dr. Kochanek that these mechanisms remain to be determined and that they may be different after traumatic brain injury.

Obrist: Patients have not yet been studied adequately for their cerebral pathophysiology after cardiac arrest. The only study I know that has measured cerebral metabolism (i.e., arterial-venous oxygen content differences in addition to cerebral blood flow measurements) in patients after cardiac arrest is the study by Beckstead et al [17]. They found hypoperfusion at 6 to 12 hrs after cardiac arrest. On the second day or later, they usually found an increased cerebral blood flow with a narrow cerebral arterial-venous oxygen content difference and poor outcome.

Marion: After cardiac arrest, there is early hypometabolism and then normal or high metabolism, starting at 1 to 2 hrs after reperfusion, according to Dr. Safar's group [13,14,24-29]. After traumatic brain injury (compression injury), Yoshino and colleagues [32] showed increased glucose metabolism in the brain in the first 20 to 30 mins after injury. If, at that time, there is low cerebral blood flow, ischemic damage is a likely outcome. These data make a strong point against hyperventilation early after brain trauma. Obrist et al. [16] described ten patients after traumatic brain injury. They showed that hyperventilation to a $PaCO_2$ of 24 torr (3.3 kPa) was associated with a global cerebral blood flow decrease to 20 to 25 mL/100 g/min and an increase of cerebral arterial-venous oxygen content difference to 10 mL/dL, which most consider characteristic of ischemia. All combined, I think that low cerebral blood flow early after brain trauma lasting for 1 to 2 days has been established. In addition, hypermetabolism at that time is a possibility [33]. We should not hyperventilate the patient during the first day after traumatic brain injury. Clinical and laboratory research results on traumatic brain injury will probably change our present practice of trying to control intracranial pressure with cerebrospinal fluid drainage, head elevation, sedation, paralysis, controlled ventilation (ideally with $PaCO_2$ guided by cerebral blood flow monitoring), osmotherapy, barbiturate administration, and hypothermia.

Kochanek: Future research must reconsider outcome measurements. So far, in laboratory studies, outcome measurements have been different for cardiac arrest vs. brain trauma vs. focal ischemia. The majority of studies of brain contusion in rats used functional outcome [34,35]. In contrast, brain ischemia rat models relied primarily on counting ischemic neurons in the hippocampus [36] and only secondarily on function. Stroke studies in various animal species depended on infarct size. In addition, autoradiographic cerebral blood flow and metabolism studies have been used in all of these insults. Probably there is much to learn from these techniques applied to different insults in different models. Cardiac arrest outcome studies in monkeys and dogs have relied on Overall Performance Categories (categories 1 to 5), Neurologic Deficit Scores (scores 0% to 100%), and semiquantitative multiregional Histopathologic Damage Scores [21,37,38].

We also need to focus on biochemical mechanisms and gene regulation. We must consider and further investigate the therapeutic window of opportunity. The therapeutic window is almost certainly shortest after cardiac arrest [21,37,38], longer after stroke [4,5], and probably longest after brain trauma [11,12,16,39]. The therapeutic window, however, needs further study.

Concerning future research, we have heard a fair amount about cerebral blood flow and intracranial pressure, but there needs to be more understanding of blood volume changes, particularly after traumatic brain injury and stroke. Traumatic brain injury frequently exhibits a clinically important window of opportunity. Intracranial hypertension often does not peak until 24 or 48 hrs after traumatic brain injury. It may be possible to develop a therapeutic strategy that could be applied early after traumatic brain injury to prevent the development of this problem. A better under standing of the mechanisms involved here, particularly in the injured brain regions where cerebrovascular failure develops, could lead to targeted treatments. Why is cerebral blood volume excessive? Why is cerebral blood flow in excess of metabolic need during the delayed periods after traumatic brain injury? Although understanding and manipulating intracranial dynamics are important, most of our present interventions are relegated to the noninjured regions of the brain. We need to do more about the injured regions if we are to achieve major improvements in outcome.

Rosomoff: Our dog data after ``brain contusion'' suggest that early intracranial pressure increase is due to increased intracranial blood volume, whereas edema comes later. Research should seek ways to decrease intracranial blood volume by means other than hyperventilation.

We have been talking about dynamic changes, but should not forget relatively fixed changes of intracranial volume compartments. These changes are in balance with each other up to a point when one or the other exceeds a critical limit, leading to an increase in intracranial pressure. We have shown that early after traumatic brain injury in dogs, the intracranial blood compartment may increase from 2.5% to 4%, which does not sound like much but can greatly increase intracranial pressure.

The initial insult is the worst because it sets off detrimental cascades. Thus, the best opportunity for therapy is in the first 1 to 2 days. However, there can be secondary insults after 24 hrs. Let us not forget how secondary extracerebral insults can influence the injured brain. Hypotensive episodes during the first 5 days after injury have been shown to worsen outcome [40]. Likewise, patients who have low jugular venous oxygen values (suggesting inadequate oxygen delivery) have been shown to have worse outcome.

Future brain trauma researchers should consider corticosteroids (and aminosteroids) for their membrane-stabilizing effects. I suggested using these agents long ago to reduce lysosome breakdown. As a curiosity, we also looked at dimethyl sulfoxide as a vehicle to bring the steroid intracellularly. Intravenous dimethyl sulfoxide in humans caused some breakdown of hemoglobin, but also caused a normalization of intracranial pressure that was similar to osmotherapy; also, following dimethyl sulfoxide, patients smelled like garlic and turned pink.

Concerning the question by Dr. Severinghaus on treating ``intractable'' intracranial pressure increases with opening the skull widely, Dr. J. Ransohoff tried this method (personal communication). This method did not seem to result in improved outcome once there was massive brain swelling. I have not tried it. I also did not use osmotherapy because that increases intracranial blood volume, which you want to avoid.

White: The protocols for the management of head-injured patients established in this country have helped a great deal. Have they revolutionized good recovery? The national head injury data bank is looking at that. We have acquired the ability to see the injury in evolution, starting with immediate CT scanning. Dr. Rosomoff used clinical intracranial pressure monitoring 35 yrs

ago. We now can find out what is going on in the brain, using CT or magnetic resonance imaging. We also have some means to affect intracranial pressure [41]. We have to start controlling extracranial variables early. Are these efforts positively affecting recovery? Which measures are important? In Holland [42], they have not used osmotherapy. However, they do monitor intracranial pressure and have superb anesthetic management and critical care. They make sure not to miss a mass lesion. Their outcome data were as good as in the United States.

CEREBRAL BLOOD FLOW

Obrist: In our study [16] of patients after traumatic brain injury, cerebral blood flow and metabolism were frequently found to be uncoupled (A6). In the early hours after severe trauma, there is a low cerebral blood flow, which is coupled to a low cerebral oxygen consumption. However, by the second or third day after trauma, uncoupling occurs; i.e., cerebral blood flow increases while metabolism remains low. Using the bedside technique with intravenous xenon-133 (^{133}) Xe) [43], we could detect unilateral and regional cerebral blood flow changes, as in subdural hematoma. Initially, there is an asymmetrically low cerebral blood flow on the side of the lesion, which then becomes progressively higher on that side during the hyperemic phase (third day).

The ability of the^{133} Xe cerebral blood flow method [43] to allow an immediate comparison between sides is valuable. Although the^{133} Xe method looks mainly at the superficial brain structures, one can differentiate between a fast (gray matter) compartment of cerebral blood flow (which normally is 80 mL/100 g/min) and a slow clearing white matter compartment (approximate 20 mL/100 g/min). Another variable to be measured is intracranial compliance (pressure/volume response), which was found to be decreased when cerebral blood volume is increased [44].

My colleagues and I [45] studied 40 patients after traumatic brain injury who remained in coma for 5 days. They all had high cerebral blood flow rates on days 2 and 3, which returned to lower values thereafter. The delayed secondary hyperemia seems to be a transient phenomenon. Some patients regained consciousness early. Patients who awakened had a return to normal flow. In those patients who died, the cerebral blood flow remained very low.

Our neurosurgeons are vigorous in maintaining intracranial pressure at less than 20 mm Hg. We found that when delayed hyperemia occurred, it was necessary to treat the majority of patients, because their intracranial pressure was more than 20 mm Hg. Treatment consisted of sedatives and paralytic agents, cerebrospinal fluid drainage, mannitol, hyperventilation (only with high cerebral blood flow), and barbiturates when other modalities were ineffective. In general, we found a rough correlation between cerebral blood flow and intracranial pressure. We can expect, on days 2 to 3, an increased intracranial pressure at the time of hyperemia, probably because of increased intracranial blood volume.

EXCITOTOXICITY

Palmer: My colleagues and 1 ([46], A7) reported evidence in rats to support the hypothesis that increased interstitial concentrations of glutamate contribute to the cell death that occurs after traumatic brain injury. Using controlled cortical impact (impact velocity equals 4 m/sec) coupled with tissue microdialysis and high-pressure liquid chromatography with fluorescence detection, interstitial concentrations of glutamate were determined in the rat frontal cortex. Moderate

injury (depth of deformation equals 1.5 mm) caused an 81 plus minus 26-fold increase (mean plus minus SEM) in dialysate glutamate concentration. Severe injury (depth of deformation equals 3.5 mm) caused a 144 plus minus 23-fold increase in dialysate glutamate concentration immediately after impact. Using interstitial concentrations of glutamate determined by Lerma et al. [47], we calculated that interstitial concentrations of glutamate increased to 231 plus minus 76 micro Meter after moderate injury and to 414 plus minus 66 micro Meter after severe injury. Since in vitro data indicate that 5 mM of glutamate is toxic [48], it is clear that the increases observed are more than sufficient to cause neurodegeneration. Trauma-induced increases in interstitial concentrations of glutamate normalized within 30 mins after moderate trauma and within 110 mins after severe trauma.

In order to establish whether the interstitial concentrations of glutamate reach toxic values after human brain trauma and whether there is a sustained or a secondary increase, we serially sampled ventricular cerebrospinal fluid from five patients (21 plus minus 2 [SD] yrs of age) with severe closed-head injury (Glasgow Coma Score equals 4.6 plus minus 1.8). Samples were collected every 4 hrs for the first 24 hrs and every 6 hrs thereafter for 3 days. Spearman's correlation analysis indicated that the cerebrospinal fluid concentration of glutamate significantly increased after injury (Rs equals 0.60; p less than .0001; n equals 42) to an average peak concentration of approximate 7 micro Meter 3 days after the initial injury [49]. Considered altogether, these data not only support the use of glutamate receptor antagonists in the treatment of brain trauma, but also suggest that sustained application may be necessary to achieve maximum therapeutic benefit.

REGENERATION

DeKoskey: My group has been interested in the brain's response to injury and the measures the brain takes in attempts at repairing itself. Alzheimer's disease, my other focus of research, includes, as does brain trauma, inflammatory cascades and reactive synaptogenesis, sprouting mechanisms, and reinnervation of denervated areas. It is known that brain interleukin (IL) concentrations increase rapidly after brain trauma [50]. Interleukins and other cytokines, produced by activated microglia, can produce both harmful and potentially beneficial effects. IL-1 beta is responsible for a number of potentially deleterious effects on brain and peripheral systems. After traumatic brain injury, IL-1 mediates a portion of postinjury brain swelling, as well as systemic hypercatabolism and hyperthermia. Interleukins can also stimulate neurotrophic factors, which would serve both to promote survival of neurons and to mitigate further cell death after trauma [51]. Nerve growth factor helps developing neurons survive and grow [52]. Nerve growth factor infused into the brains of normal adult animals or into old animals (which have a natural loss of cholinergic enzymes) caused up-regulation of cholinergic enzymes and improved behavior and memory test results [53]. Another possible role for nerve growth factor in the brain is the up-regulation of antioxidant enzymes in neurons, which may be very important in the brain's response to injury from free radicals. This upregulation has not yet been measured in old animals. We hypothesize that, whatever stimulates the production of nerve growth factor (e.g., an inflammatory reaction) would benefit the brain after traumatic brain injury. A therapeutic goal might be cytokine blockade coupled with infusion of an appropriate neurotrophin. Besides hypothermia having a positive effect by suppressing inflammation and other detrimental cascades early, hypothermia might also have a negative effect by depressing the formation of nerve growth factor and reducing later regeneration.

We are examining the role of IL-1 beta and other cytokines, as well as nerve growth factor after neurotrauma. The goal is

to identify whatever could help regeneration or synaptic regrowth. We first studied patients after traumatic brain injury [54] and found, as expected, an increase in the ventricular cerebrospinal fluid concentration of IL-1, concentrations higher than those values found in peripheral blood. These concentrations were lower in hypothermic patients.

In cultured neurons and neuron support cells, IL-1 up-regulates and stabilizes the ribonucleic acid (RNA) of nerve growth factor [55]. We applied this concept to our rat brain cortical contusion model. We showed that mRNA for nerve growth factor was increased on day 1 after trauma and that it was decreased to normal concentrations by days 3 to 5. There is currently no way to quantify rat IL-1 protein. Therefore, we infused human IL-1 into rats, which caused an increase in nerve growth factor [51]. My colleagues and I [56] then demonstrated that stopping the production of IL-1 with hypothermia (as shown in patients) suppressed nerve growth factor in rats. In our rat model, 4 hrs of hypothermia after brain trauma resulted in total suppression of nerve growth factor and its mRNA. We thus suspect that hypothermia in patients might suppress neurotrophins.

We [57] also obtained genetically modified rabbit fibroblasts that secrete a blocker of IL-1, and which, when infused into injured brain, block the up-regulation of nerve growth factor protein by 50%. Is it possible to do good without hypothermia? If we suppress inflammation, we may have to provide another stimulus for nerve growth factor up-regulation or directly infuse it into the injured brain. We are now looking at measures of synaptic loss after injury to determine if infusing nerve growth factor (which otherwise would be suppressed by hypothermia or other anti-inflammatory treatments) results in better outcome after traumatic brain injury. For this approach to become effective, behavioral outcome studies are needed.

Reasons for blocking the effects of IL-1 (by hypothermia or other means) include the secondary (deleterious) effects of IL-1 on immune responses--creating a hypercatabolic state and hyperthermia--and the overall effects of IL-1 on white blood cells.

PREHOSPITAL RESEARCH

Safar: Since my work with emergency medical services in Baltimore in the 1950s, I suspected from ambulance reports the occasional occurrence of ``impact apnea'' immediately after traumatic brain injury. This phenomenon has been confirmed through others' laboratory data [58,59]. Impact apnea is breath-holding during the first 1 to 2 mins of coma after impact to the head. This breath-holding is long enough to cause decreased PaO_2 and increased $PaCO_2$ (presumably worsening the subsequent brain swelling), but not long enough to cause cardiac arrest. Spontaneous hyperventilation then follows, driven by acidosis and the initial response of the brain to injury. However, there can be partial or complete airway obstruction as a result of coma in the absence of backward tilt of the head, or as a result of aspiration. Another topic for clinical and laboratory research is the immediate postimpact catecholamine surge, which can cause deleterious severe hypertension [60,61]. These reactions represent challenges for bystanders to immediately treat traumatic brain injury victims, as necessary, with head tilt and jaw thrust, and with exhaled air ventilation (which in trismus must be via mouth-to-nose) and for ambulance paramedics to control arterial pressure at an optimal level, which is still to be determined. Hypotension can worsen secondary ischemia, while severe hypertension can worsen secondary hemorrhage and edema. Young clinical traumatic brain injury investigators should move some of their studies as close as possible to the moment of impact, into the prehospital arena (A8). The earlier the secondary derangements after traumatic brain injury are controlled, the less likely will prolonged, expensive intensive care be necessary.

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