not improve sensory as much as motor function. It is important to recognize two discrete time parameters: 1) the time to initiate methylprednisolone treatment (the 8-hour window); and 2) the duration of treatment (24 hours). Based on the animal study data and pharmacodynamics of methylprednisolone, we hypothesize that, when treatment is started after 8 hours, secondary injury due to lipid peroxidation and other manifestations of injury progression is so advanced that it cannot be influenced by the 30-mg/kg dose. Moreover, there may be immunosuppressive effects of this high dose of methylprednisolone which, if given too late to affect secondary injury, may have a deleterious effect on normal recovery. The second NASCIS does demonstrate a "rational pattern of recovery" in that partial injuries do "respond best." This continues to be evident in the 1-year results published in our paper (Table 5).

The fourth point referred to groupings of results. The correct combination of data from Table 5 were reported as the primary results in our paper (text, p 26), namely: motor change scores 17.2 versus 12.0 for the methylprednisolone and placebo groups, respectively (p = 0.03). There are not 27 comparisons in Table 5; in fact there are six independent comparisons (the motor pinprick and touch sensation parameters are highly correlated), and all 18 comparisons are prespecified hypotheses and validly tested at the usual levels of significance. The categories of spinal cord injury severity were established a priori and are the same as those used in NASCIS 1.

Dr. Rosner's fifth point is answered above in our response to Dr. Shapiro.

There is a generic problem through all of medicine where currently accepted methods of treatment may interfere (by synergism, interaction, or effect-cancellation) with proposed new therapies. However, it is within the confines of properly designed and conducted controlled clinical trials that innovative treatment comparisons appropriate for the proposed mode of action must be designed and ethically administered. This affords protection to the patient from inappropriate treatment and to the physician from medicolegal imperatives. The third NASCIS, which is in the process of enrolling almost 500 patients, is comparing tirilazad mesylate against methylprednisolone by giving the former after a single bolus of the latter, and without concurrent use of both drugs.

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References

Comparability of Vasospasm in Primates

TO THE EDITOR: This letter is written in regard to a recent paper (Macdonald RL, Weir BKA, Young JD, et al: Cytoskeletal and extracellular matrix proteins in cerebral arteries following subarachnoid hemorrhage in monkeys. J Neurosurg 76:81-90, January, 1992). Because smooth-muscle relaxing agents have no effect on cerebral vasospasm and balloon angioplasty seems to work well, many (like these distinguished investigators) are now seeking causation beyond the smooth-muscle medial layer. However, we believe that they misinterpreted the results of our work in human cases which they cite.

Throughout the discussion, reference is made to a failure to identify any increase in deposition of collagen based on analysis for hydroxyproline, but ample reference was made to increased staining, in the intima, for the various collagen types at stages of increased vasospasm. Although these data for the intima were not included in their Table 3, it is clear from their description in the text and from their photomicrographs that substantial amounts of the collagens are present. Figure 1 even seems to indicate quite clearly increased staining of types I and III collagen at Day 28. This might seem to suggest some problems with the hydroxyproline assay; however, quite another explanation is possible. An apparent increase in staining intensity might demonstrate a rearrangement of the collagen fibrils into a more compact mass. This reorganization of the existing matrix would not require an increase in molar mass amounts of collagen during severe vasospasm, and no increases in hydroxyproline would be detected. Fibril...
compaction could easily be responsible for constriction of vessels in the vasospastic state. This mechanism has been suggested in publications and presentations from this laboratory and demonstrated experimentally in culture models of human cerebral artery myofibroblasts in collagen matrices similar to those found in cerebral vessels.

The authors relate the increases in intima collagen after subarachnoid hemorrhage (SAH) to a role for fibrosis in arterial wall stiffening and, by implication, a role in maintenance of vasoconstriction initiated by the smooth muscle. Collagen reorganization (compaction) by myofibroblasts may not require any additional material deposited into the extracellular matrix by those (or other) cells. No "glue" would be needed by the cells to help cross-link the collagen. They suggest such a role for the increased amounts of fibronectin in spastic vessels. However, fibronectin has not been implicated in collagen cross-linking. The actual (and apparently more significant) role for fibronectin is in cell attachment to collagen in functions such as migration or (in a similar cell mechanism) collagen matrix reorganization (compaction of collagen lattices).

The authors also suggest that to implicate collagen in a role in the vasoconstrictive process requires demonstrating its removal as part of the process to restore the normal state. Demonstration of changes in vascular wall composition or organization during vasospasm is easier to accomplish than demonstration of "reversal" of fibrosis as vasospasm resolves. Perhaps these studies could be attempted in animals, but it is difficult or impossible in humans, as tissue samples of cerebral vessels are available for study only at autopsy. Because resolution of vasospasm usually means that the patient survived, examination of the structural organization of cerebral arteries after vasospasm resolves could happen only very infrequently and without controlled conditions.

In their paper, Macdonald and his coworkers summarily dismiss the role of myofibroblasts, indicating that mammalian muscular arteries do not contain fibroblasts except in the adventitia. This may be true under normal circumstances but, without question, they appear after SAH. We have now cultured subintimal myofibroblasts from arteries of five human cases of post-SAH vasospasm after removal of the adventitia. In multiple trials, we have not been able to culture myofibroblasts from arteries of human patients who died of other causes, and thus we conclude that the myofibroblastic reaction is unique to SAH. In all post-SAH cases, the cells were cultured before Day 9 and as early as the 2nd day after SAH. The question arises as to why type V collagen and myofibroblasts are identified early in human cases and why they are absent or appear much later in the monkey. Perhaps it is important that none of the nine monkeys described in the paper under discussion, only a few myofibroblasts have proliferated by the 7th day post-SAH because either the animal does not get the disease as we see it in humans or the SAH was not as severe as seen in postmortem human tissue. Macdonald, et al., found increased amounts of type V collagen in the thickened intima late after SAH, just as we found this protein much earlier in our human cases. The discrepancies in the observations in the human and monkey cases may be a matter of severity of the lesion and species differences.

As stated by the authors, the morphological distinction between a myofibroblast and a smooth-muscle cell of synthetic phenotype seems to blur. The difference in mechanism of action (contraction), however, is an important one. Smooth-muscle cells in vessel walls are attached to the basement membrane and in response to nerve impulse or transmitter release. The myofibroblast is a migratory cell responding perhaps to wound hormones, such as platelet-derived growth factor, transforming growth factor-β, and possibly to other agents that are yet unidentified. If true, there must be some stimulant peculiar to the cerebral environment since peripheral vasospasm is rarely seen, even in vessels surrounded by thick blood clot.

These differences also address the problem of the lack of appropriate animal models for the uniquely human type of delayed-onset vasospasm. There are, in fact, no adequate animal models. Animals simply do not develop vasospasm in the way humans do, just as animals do not heal wounds in the same way. Wound healing in humans is most often accomplished by a fibrosis-like scar formation, whereas animals close wounds by an active "wound contraction" process. This latter process also involves myofibroblasts rearranging collagen matrices to a more compacted organization, thus effecting an overall reduction of the area of the wound without cell shortening (cell contraction).

This species difference in response to injury, without doubt, is significant to the post-SAH vasospasm problem and its study in a research setting. It is difficult to draw information from animal models that could be vitally useful in a human treatment sense. It is very likely that the process is different in humans and animals. Herein lies the basic difference between the direction of research in their laboratory and ours, as well as in the postulated mechanisms. The group in Edmonton views the post-SAH differences in vascular wall structural components as the result of injury due to prolonged vasospasm rather than as the cause (or direct contributing factors) of the vasospasm. Because of the lack of animal models to study this phenomenon adequately and appropriately, we must instead rely on gaining an understanding of the cell biological processes involved on a final scale. This goal is being approached by studies in our laboratory through culture models using human myofibroblasts from vessels obtained at autopsy from patients with severe, clinically significant vasospasm.
Neurosurgical forum

The authors should be congratulated on this excellent contribution and should be encouraged to pursue these studies further. However, the supreme mammalian model for cerebral vasospasm, the human case, should also be examined for matrix protein changes using methods similar to those in their paper.

Robert R. Smith, M.D.
David H. Bernanke, Ph.D.
University of Mississippi Medical Center
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RESPONSE: Drs. Smith and Bernanke raise several issues. We agree that there is increased collagen in vasospastic arteries, although we could only detect it more than 14 days after subarachnoid hemorrhage, at a time when vasospasm was resolving. We suggested that changes in the extracellular matrix, which could include the "fibril compaction" theory, may develop in vasospastic arteries and contribute to persistence of arterial narrowing. Since the methods used in our study would not detect such changes, we do not know when or whether these processes develop. The conclusion states this.

Smith and Bernanke believe that the monkey model does not produce vasospasm akin to that occurring in man. It will be difficult, however, to study the entire time course of vasospasm in man using detailed biochemical and histological techniques. Animal models help fulfill this role, and the monkey model produces vasospasm that is generally regarded as quite similar to vasospasm in man. Many experimental results obtained in monkeys have been substantiated in humans.1,2 One can never be sure, of course, that differences between primates exist, but we suspect that they are minimal and that the underlying mechanisms are similar. There appears to be some controversy about differences in wound healing between animal species. Some authorities believe the mechanisms are essentially the same, but that local anatomical differences (for example, in the mobility of the skin) alter the relative contributions of the various processes to the healing of a wound.4

The diminishing distinction between myofibroblasts and proliferating smooth-muscle cells has been mentioned. Most authors believe proliferating intimal cells in injured arteries are derived from medial smooth muscle.1 Smith and Bernanke believe human cerebral arteries in vasospasm generate a distinct cell, the myofibroblast. Clearly, cells do appear in the intima, even in monkeys. The exact nature of these cells, and their contribution to vasospasm, remains to be determined. This work will involve studies in humans and in animal models.

References


Cruciate Paralysis

To The Editor: Since I have no truck with psychoanalysis, I have no ready hypothesis to explain the extraordinary preoccupation of my neurosurgical colleagues with the alleged phenomenon of “cruciate paralysis.” Dr. Coxe and I are pleased that the recent elegant study of the pyramidal tract decussation in squirrel and cynomolgus monkeys by Pappas, et al (Pappas, CTE, Gibson AR, Sonntag VKH: Decussation of hind-limb and fore-limb fibers in the monkey corticospinal tract: relevance to cruciate paralysis. J Neurosurg 75:935–940, December, 1991), confirmed our primitive findings. But this is my third letter to the editor of a neurosurgical journal about cruciate paralysis.1–3

Realizing their truly convincing negative result, Pappas, et al, must stretch far to fancy some magical connection of the medullary gray matter or the ventral corticospinal tract. Paraphrasing Shakespeare, “The fault, dear Friends, is not in our stars, but in ourselves.” The evidence that “damage in the region of the cervicomedullary junction of humans does affect the limbs differentially” just ain’t there. None of the alleged cases was subjected to pathological study. Most of them were observed in patients with severe closed head injuries. Now that we are well into the magnetic resonance imaging era, no case with a tidy little unilateral medullary lesion has been described. Until that happens, one may reasonably plead for an editorial “kibosh” upon this pseudo-subject.

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