ABSTRACTS of the Vth INTERNATIONAL SYMPOSIUM ON CEREBRAL VASOSPASM

SESSION A

Epidemiology of Vasospasm

1 SYMPTOMATIC VASOSPASM AFTER ANEURYSMAL SAH H. Säveland, J. Hillman, L. Brandt, K.-E. Jakobsson, G. Edner, G. Algers. Departments of Neurosurgery, University Hospitals in Lund, Linköping, Gothenburg, Stockholm and Umeå, Sweden.

The present prospective study, with participation of five of the six neurosurgical centers in Sweden, was conducted to evaluate our overall management results in aneurysmal SAH. Six million nine hundred thirty thousand (6.93) of Swedens 8.59 million inhabitants (81%) were covered by the participating centres . All patients with verified aneurysmal SAH admitted between June 1 1989 and May 31 1990, were prospectively collected. A uniform management protocol was adopted including ultra-early referral, earliest possible surgery and aggressive anti-ischemic treatment. A total of 325 patients were admitted, 69% within 24 hours after the bleed. Upon admission the patients were graded according to Hunt&Hess: 43 patients (13%) were grade I, 119 (37%) in grade II, 53 (16%) in grade III, 76 (23%) in grade IV and 34 (10%) in grade V. Nimodipine was administered in 269 of the 325 patients.

Surgery was performed in 276 (85%) of the patients. Early surgery, ie within 72 hours after the bleed, was performed in 170 individuals. At follow-up 3-6 months after the bleed 183 patients were classified as having made a good neurological recovery (56%) , 73 patients suffered from morbidity (23%) and 69 were dead (21%).

In 19 patients (5.8%) the unfavorable outcome was caused by delayed cerebral ischemia. However, three other causes had more victims; the initial bleed (65patients, 20%), rebleeding (20, 6.2%) and surgical trauma (20, 6.2%).

Furthermore, we will present details concerning the relationship between age, preexisting arterial hypertension, clinical grade on admission, CT-grading according to Fisher, timing of surgery and localisation of the ruptured aneurysm to the occurrence of symptomatic vasospasm.

2 **Withdrawn.**

3 CLINICAL STUDIES IN VASOSPASM: ONSET AND PROGRESSION

Y.N. Zubkov, R.R. Smith*. A.L. Polenov Neurosurgical Institute, St. Petersburg, Russia; Department of Neurosurgery*, University of Mississippi Medical Center, Jackson, Mississippi 39216-4505.

This study consists of 232 consecutive patients who developed cerebral vasospasm following rupture of an intracranial aneurysm between 1972 and 1992.

Two types of onset characterized this group of patients: gradual and apoplectic. The gradual type of onset was more commonly seen in patients in the compensated state (Hunt & Hess grades I & II); it rarely occurred in higher grade patients. Both generalized and focal neurological symptoms characterized the progressive course developing over several days. Brainstem dysfunction included deteriorating levels of consciousness, loss of upward gaze, and loss of gag and corneal reflexes. During this stage, intracranial pressure increased minimally.

The apoplectic type developed most commonly in patients in higher grades. Onset occurred over minutes or hours, sometimes simulating rebleeding. The signs involved both consciousness and the motor systems and were usually profound. Intracranial pressure was usually elevated significantly in this group but did not rise precipitously with the event.

The brain stem signs associated with the insidious form, in our opinion, are directly attributable to involvement of short penetrating arteries. This observation was confirmed by xenon blood flow studies scintiangiography.

4 ANGIOGRAPHIC VASOSPASM IN THE NINETIES- A CONTINUING PHENOMENON. T.J. Coyne, R.L. Macdonald, M.C. Wallace. Division of Neurosurgery, The Toronto Hospital,University of Toronto, Toronto, Canada.

The past 15 years have seen significant changes in the management of patients with aneurysmal subarachnoid haemorrhage (SAH). Many of these changes, such as management of fluids and blood pressure and the use of calcium channel blockers, have been directed at the prevention and treatment of vasospasm. The angiograms of a contemporary series of 56 consecutive surgically treated patients with aneurysmal SAH were examined to compare the pattern and degree of angiographic spasm with that of previous studies. 37 patients (76%) were WFNS grades 1-2. A ratio of subarachnoid vessel calibre to that of the same vessels extracranially at the skull base was plotted against day of angiogram. This demonstrated that the time course of angiographic spasm remains unchanged from that of previous series, with onset at day 4, maximal spasm during the second week, and resolution after day 16.

30% of patients had clinical vasospasm (delayed neurological deficit for which other causes had been excluded), and these patients had more severe angiographic narrowing than those without clinical spasm, particularly in the second week post SAH (mean ratio value 1.42 v 1.73, $p < .05$). 44 angiograms were performed between days 1-3 post SAH and repeated between days 4-16. 95% of these showed narrowing at the second angiogram, with an average ratio reduction of 21%. Patients not achieving independence showed a trend towards having had both clinical vasospasm and more severe angiographic vasospasm, although this did not reach statistical significance. We conclude that angiographic spasm remains a common occurrence in the modern era, and continues to be associated with clinical events and poor outcomes.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

5 CEREBRAL VASOSPASM AFTER ANEURYSMAL SAH IN ELDERLY PATIENTS

V. Rohde, B. Meyer, K. Schaller, W. Hassler
Dep. of Neurosurgery, Klinikum Kalkweg, Duisburg, Germany

Introduction: Recent **angiographic** studies report that the degree of cerebral vasospasm after aneurysmal subarachnoid hemorrhage (SAH) in elderly patients is not different from that in younger patients (Inagawa 1992). Reduced CO_2-reactivity of cerebral arteries was demonstrated in elderly by means of **transcranial Doppler sonography** (TCD) (Hassler 1986), suggesting reduced vessel reactivity to vasoactive substances released during SAH. Objective of the study was the Doppler sonographic investigation of age-dependency of cerebral vasospasm after aneurysmal SAH.

Patients, methods: In 1oo patients under 6o years and 5o patients over 6o years, who had been operated on after aneurysmal SAH, serial TCD examination of the basal cerebral arteries were performed; blood flow velocities between 12o and 16o cm/s were defined as moderate vasospasm, over 16o cm/s as severe vasospasm.

Results: 19% of the patients over 6o years, but 5o% of the patients under 6o years developed cerebral vasospasm. Permanent symptomatic vasospasm only occured in younger patients (7 %).

Conclusion: Cerebral vasospasm is significantly less frequent in elderly patients, possibly due to reduced reactivity of arteriosclerotic vessels to vasoactive substances released during SAH.

6 CEREBRAL VASOSPASM FOLLOWING SUBARACHNOID HEMORRHAGE CORRELATES WITH AGE OF PATIENTS

H.G. Böcher-Schwarz, K. Ungersböck, P. Ulrich, G. Fries, A. Perneczky Division of Neurosurgery, University Mainz, Germany

A study was performed to determine whether cerebral vasospasm following subarachoid hemorrhage correlates with the age of the patients. For at least 3 weeks after bleeding 80 subjects underwent very close follow-up with clinical examination and transcranial Doppler records of the blood velocities within the basal cerebral arteries.

According to their age and the maximum of recorded mean velocities (v), the patients were divided into groups as follows: age 55 years or less, age more than 55 years; and mean velocity v1<90cm/s, 90cm/s<v2<120cm/s, 120cm/s<v3<160cm/s, v4>160cm/s .

With regard to the mean velocities there was a significant (chi-squared statistic for contingency tables, alpha 0.01) difference between both age-groups: 32% (n=18) of the younger fell into group v4 with maximum mean velocities of more than 160cm/s, but none of the older had such. Vice versa, 62,5% (n=15) of the older compared with only 14,3% (n=8) of the younger fell into group v1 with maximum mean velocities of less than 90cm/s. Clinical follow-up also depicted differences between both age groups. 13 of 18 younger patients with maximum mean velocities > 160cm/s exhibited symptomatic vasospasm with a delayed neurological deficit. This typical course did not occur in the older age group.

We conclude from this study that the increase of blood velocity in the basal cerebral arteries following subarachoid hemorrhage depends on the age of the patient. Furthermore, young patients will be more prone to a delayed ischemic deficit. On the other hand, older patients may also suffer for ischemic deficits following subarachnoid hemorrhage but without measurable vasospasm according to transcranial Doppler criteria and without the typical delayed appearance.

7 A RELATIONSHIP BETWEEN VASOSPASM AND LOW DENSITY AREAS IN CT SCANS SECONDARY TO VASOSPASM

A. Masago, K. Kamiya, H. Nagai, Department of Neurosurgery, Nagoya City University, Medical School, Nagoya, Japan.

In order to clarify the difference between low density after vasospasm and that of cerebral infarction, low density areas in CT scans were studied as follows. **<Methods>** Low density areas secondary to vasospasm were investigated by CT scans, in 359 patients with aneurysmal SAH who admitted to our department since 1978 to 1991. We divided the low density areas in CT scans into 3 groups. Group 1: low density area involved the cortex and white matter as well as cerebral infarction. Group 2: low density area sparing the cortex. Group 3: low density area involved the basal ganglia and other perforating arterial territory. **<Results>** The extent and location of subarachnoid clot were correlated well with subsequent low density areas. Low density areas were found mainly in the white matter in the appropriate major arterial territory adjacent to Sylvian fissure and infrequently in the basal ganglia fed by perforating arteries. In some cases of huge cerebral ischemia including major arterial territory, CT scans showed mottled distribution of low densities sparing the cortex. It might be possible to say that there was considerable amount of viable brain tissue which could be saved in the low density areas. **<Conclusions>** We would like to stress an importance of aggressive treatment for vasospasm to save the scattered viable brain tissue in the ischemic lesion and to reduce the size of low density areas after vasospasm.

SESSION B
Detection and Monitoring of Vasospasm and Brain Ischemia after Subarachnoid Hemorrhage

8 AUTOREGULATION AS ASSESSED BY THE TRANSIENT HYPERAEMIC RESPONSE TEST (THRT) IN PATIENTS WITH SUBARACHNOID HAEMORRHAGE(SAH).

J D Pickard, V Iyer, M Czosnyka, H Whitehouse, P Kirkpatrick.
Academic Neurosurgery Unit, Level 4, A Block, Addenbrooke's Hospital, Cambridge, CB2 2QQ.

The development of delayed cerebral ischaemia after SAH is partly related to the loss of cerebral autoregulation[1] as assessed using radionuclides. We have evaluated the role of the transcranial Doppler (TCD), in the assessment of autoregulation after aneurysmal SAH. Theoretically, the transient increase in middle cerebral artery (MCA) blood flow velocity (FV) after brief common carotid artery (CCA) compression, relates to the strength of autoregulation[2].

Bilateral MCA flow velocities and arterial blood pressure were monitored daily in 50 SAH patients before and after a 3 second compression of the CCA. Measurements were made of Flow Velocity (FV), Pulsatility Index (PI), and the THRT.

A negative THRT was found to correlate with a poor clinical (Hunt & Hess) grade and a worse Glasgow outcome. The likelihood of a positive THRT decreases as the FV increases above 150 cm/sec and is least in the second week after the bleed.

The THRT as an index of autoregulation provides useful additional information to clinical grade and DFV alone.

[1]Pickard JD, Matheson M, Patterson J, Wyper D, J Neurosurg. (1980) 53:305-308.

[2]Czosnyka M, Pickard J D, Whitehouse H, Piechnik, Acta Neurochir. (1992) 115: 90-97.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

9 THE INFLUENCE OF VARIOUS FACTORS ON TRANCRANIAL DOPPLER FLOW VELOCITY AND RESISTANCE INDEX AFTER SAH. A. Pasqualin, G. Pavesi, R. Battaglia, G. Acerbi. Department of Neurosurgery of Verona, and Division of Neurosurgery of Cesena (R.B.) and Pescara (G.A.), Italy.

Eighty-eight patients with aneurysmal rupture (admission time 0-3 days from SAH) were evaluated with serial transcranial Doppler (TCD) recordings in the first 15 days from SAH. All patients received nimodipine. The main end-point considered were the highest time-mean velocity resistance index (RI) on the middle cerebral artery during the following intervals: 0-1, 2-3, 4-6, 7-9, 10-12, 13-15 days from SAH. Particular attention was paid to conditions possibly linked with increased intracranial pressure, such as poor admission grade, intracerebral hematoma, hydrocephalus, and focal cerebral edema. At 0-3 days, patients graded IV to V exhibited significantly lower (p=0.01) velocity than patients graded I or II, with a significantly higher RI - at 0-3 and 4-9 days - than all other patients. Patients with large hematomas showed a markedly lower velocity and a markedly higher RI at 0-3 and 4-9 days. Patients developing hydrocephalus exhibited - at 0-3 days - a significantly lower velocity (p=0.01) than all other patients. Patients operated on early (n=54) showed a significantly higher velocity - at 4-9 and 10-15 days - than the other patients, with a slightly higher RI. Although the group of patients with clinical deterioration from spasm showed a significantly higher velocity (~ 140 cm/sec) at 4-9 and 10-15 days (with a markedly lower RI at 4-9 days), a few cases showed a normal velocity, in one case associated with a very high RI. In conclusion, since many factors may influence TCD parameters in the early stage of SAH, the value of blood velocity alone can be inadequate to assess the presence and severity of cerebral vasospasm.

10 AMOUNT OF SUBARACHNOID BLOOD RELATED TO VASOSPASM C. Schaller, V. Rohde, B. Meyer, W. Hassler
Dept. of Neurosurgery, Duisburg, Germany

According to the literature, the amount of subarachnoid blood correlates with occurence and severity of cerebral vasospasm after aneurysmal SAH. Most of these studies however have been undertaken in the pre-TCD-era. Is it still true, that FISHER grade of SAH correlates with the degree of vasospasm ?

98 patients, who underwent aneurysm clipping up to 96 hours after SAH were followed daily with TCD. Admit CT scans were graded according to FISHER. Blood flow velocities between 12o and 16o cm/s were defined moderate spasm, greater than 16o cm/s severe vasospasm.

In the FISHER grade I group (n=26/26,5%), n=11 (42,3%) had severe vasospasm, n=7 (26,9%) moderate and n=8 (3o,8%) none. In the FISHER grade II group (n=35/35,7%), n=9 (25,7%) had severe spasm, n=13 (37,1%) moderate and n=13 (37,1%) none. In FISHER grade III patients (n=37/37,8%, n= 13 (35,1%) had severe spasm, n=1o (27%) moderate and n=14 (37,8%) none. Time of surgery (less than 24 hs. vs. 48 hs. vs. 96 hs. after SAH) did not affect these results.

Our results suggest, that it is obsolete to rely on the amount of subarachnoid blood as a predictor for the occurence of vasospasm. The time of early surgery (24vs. 48 vs. 96 hs.) also doesn't alter the individual prognosis for occurence of vasospasm.

11 PATTERNS OF LINEAR BLOOD FLOW VELOCITY ASYMMETRY FOLLOWING SUBARACHNOID HEMORRHAGE A.Ye. Razumovsky, A. Lee, M.A. Williams, H. Nauta, D.F. Hanley
Departments of Neurology and Neurosurgery, Johns Hopkins Medical Institutions, Baltimore, MD 21287

Increased linear blood flow velocity (LBFV) in the middle cerebral artery (MCA) has been associated with symptomatic vasospasm after aneurysmal subarachnoid hermorrhage (SAH), but the ability of transcranial Doppler (TCD) sonography to identify lateralized changes in vasospasm has not been well studied. We examined 49 consecutive patients to determine the temporal and symmetry pattern changes of LBFV that occur after SAH. Study results were grouped into 3-day bins (day 0-2, 3-5, etc) for comparison over time. LBFV in corresponding ispsilateral/contralateral vessel segments were compared to assess symmetry. Results were analyzed with ANOVA and nonparametric tests, with the significance level set at $p \leq 0.05$.

LBFV increased significantly in the MCA M1 segment bilaterally from day 6-20. LBFV was also increased in both internal carotid artery (ICA) C1 segments from day 9-14 and day 18-20. There was no consistent LBFV increase in anterior cerebral or ophthalmic arteries. Assessment of asymmetry showed contralateral M1 LBFV was higher than ipsilateral M1 LBFV from day 0-5, but not afterwards. Ipsilateral C1 LBFV was higher than contralateral C1 LBFV from day 3-14. There was no asymmetry of LBFV between the A1 segments. These findings confirm earlier reports that M1 LBFV rises significantly and bilaterally during the risk period for vasospasm and also shows a similar increase in C1 LBFV. In addition, there is significant asymmetry of C1 LBFV, which is consistently higher on the side of the ruptured aneurysm. There is no asymmetry of M1 LBFV. We speculate that C1 LBFV asymmetry reflects anatomic narrowing of the ICA lumen at its bifurcation which may increase the risk of reducing cerebral blood flow below ischemic thresholds in more distal vascular distributions.

12 EARLY DETECTION OF SYMPTOMATIC VASOSPASM FOLLOWING SUBARACHNOID HEMORRHAGE USING TCD, SPECT, CoBF MEASUREMENTS K. Iric, Y. Honma, H. Kuyama, S. Nagao. Department of Neurological Surgery, Kagawa Medical School, Kagawa, Japan

Recently non-invasive and serial measurement of flow velocity of the cerebral arteries using transcranial doppler ultrasonography (TCD) has been employed for detection of symptomatic vasospasm (SV) following subarachnoid hemorrhage (SAH). However, its reliability has not been established. In addition to TCD, we employed 2 monitorings, ^{99m}Tc-HMPAO single photon emission CT (SPECT) for cerebral blood flow (CBF), and laser doppler flowmeter for cortical blood flow (CoBF). A usefulness of these combinations for the prediction of SV following SAH was determined. In 15 patients, the mean flow velocity of the middle cerebral artery (M1) was measured daily for 14 days after SAH with TCD. CBF was measured 2-3 times with ^{99m}Tc-HMPAO SPECT for 14 days after SAH. C/C ratio (cerebral hemisphere ROI counts/cerebellar hemisphere ROI counts) and cerebral vasodilatory capacity with intravenous acetazolamide were calculated from SPECT images. CoBF was measured continuously with laser doppler flowmeter for 7 to 10 days after surgery. The probe was placed on the cortical surface of MCA (middle cerebral artery) territory. In patients with SV, rapid increase in MFV over 120 cm/sec, decreased C/C ratio less than 0.8, impaired vasodilatory capacity, and low CoBF less than 30 ml/100g/min were characteristic. These results suggest that serial examinations of MFV, CBF and CoBF with combination of TCD ultrasonography, SPECT and laser doppler flowmeter are useful for prediction of SV.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

13 LONG-TERM EVALUATION OF PATIENTS WITH VASOSPASM BY TRANSCRANIAL DOPPLERSONOGRAPHY AND TC-99m-HM-PAO-SPECT

A.Reinprecht, T.Czech, M.Schmidbauer, I. Podreka. University of Vienna Medical School, Dept. of Neurosurgery and Dept. of Neurology Vienna, Austria

Histological studies of large intradural arteries in autopsy cases of patients dying 4 weeks or later after spontaneous subarachnoid hemorrhage (SAH) due to an intracranial aneurysm showed structural changes of the arterial wall with intimal thickening by subendothelial fibrosis. Assuming that this process would lead to constant intraluminal narrowing of the involved arteries in surviving patients and to maldistribution of cerebral perfusion we performed a follow-up study using transcranial dopplersonography (TCD) and 99m-technetium-HM-PAO single-photon emission computed tomography (SPECT) of young patients 1.5 to 5 years after aneurysm surgery following SAH.

Twenty-nine patients, 15 male and 14 female, aged between 28 and 40 years (mean age 36.2 years) underwent TCD-examination. None of them had cerebrovascular disease risk factors. All were operated within the first 72 hours after SAH. Aneurysm site was anterior communicating artery (ACoA) in 12 cases, middle cerebral artery (MCA) in 10 cases, internal carotid artery (ICA) in 9 cases, anterior cerebral artery (ACA) in 1 case and basilar artery in 1 case. Four patients had multiple aneurysms. All patients developed vasospasm in the postoperative period diagnosed by TCD with mean flow velocities (MFV) over 110 cm/sec. At the time of follow-up (1.5 to 5 years) 23 patients had recovered completely and 6 showed mild neurological deficit. Out of these 29 patients 10 were studied in Tc-99m-HM-PAO-SPECT before and after intravenous injection of acetazolamide. None of them showed neurological deficits.

TCD showed MFV in the normal range (<80 cm/sec) in 12 patients, slightly increased (80-110 cm/sec) in 15 patients and above 110 cm/sec in 2 patients. SPECT showed focal reduction of uptake in 3 cases, diffuse reduction in 1 case and focal and diffuse reduction in 5 cases. Only one patient showed a normal activity pattern. Focal reduction was related to the site of aneurysm in 2 cases, in 6 cases there was no relation. In patients with focally reduced uptake, acetazolamide increased uptake in 5 cases but decreased uptake in 3 patients.

Our initial results suggest that structural changes in intradural arteries following vasospasm after SAH may lead to changes in cerebral blood circulation with areas of reduced perfusion in young healthy patients without functional deficit.

14 QUANTIFICATION OF REGIONAL CEREBRAL BLOOD FLOW WITH HMPAO-SPECT AFTER SUBARACHNOID BLEEDING AND VASOSPASM

H. Eichstaedt, M. Cordes, R. Reyes, O. Danne

Departments of Cardiology and Angiology, Department of Radiology, University Hospital Rudolf Virchow, Free University of Berlin, Germany

We investigated 24 patients (12 m, 12 fm) in an early stage (up to 14 days, group 1) and in a late stage (after 40 days, group 2) after subarachnoid bleeding. The mean age in group 1 was 49.7 years ± 16.8 and in group 2 41.9 years ± 21.6. Measurement of regional cerebral blood flow has been investigated by single-photon-emission-computer-tomography (SPECT) 10 minutes after injection of 740 MBq 99mTc-HMPAO. Cerebral perfusion was measured by counts per matrixpoint. Disturbances of perfusion have been found in the ipsilateral cortical region in group 1 in 8 of 9 patients and in group 2 in 12 of 15 patients ($p = 0.572$, chi-quadrat test).

In the contralateral cortical region we found disturbances of perfusion in group 1 in only 4 of 9 cases and in group 2 in 2 of 15 patients ($p = 0.088$).

Different results could be found in cerebellar perfusion: ipsilateral disturbances were found in group 1 only in 3 of 9 patients and in group 2 in none of 15 patients ($p = 0.017$). Contralateral cerebellare blood flow disturbances could be shown in group 1 in none of 9 patients and in group 2 in only 1 of 15 patients ($p = 0.429$).

In result, regional disturbances of perfusion can be demonstrated as well in early as in late stages after bleeding in cortical regions. However, ipsilaterale cerebellare decrease of perfusion is found much more often in early stages after bleeding. SPECT-measurement is a very reliable method for quantification of blood flow after bleeding and vasospasm.

15 Cerebral blood flow and cerebrovascular reserve capacity in patients with subarachnoid hemorrhage.

Ryuta Suzuki, Tadashi Nariai, Tuneo Shishido, Tutomu Asano, Kimiyoshi Hirakawa.
Department of Neurosugery, Tokyo Medical and Dental University, Tokyo Japan.

In order to observe the effect of subarachnoid hemorrhage (SAH) to cerebral blood flow (CBF) and cerebrovascular reserve capacity, we performed xenon-enhanced CT (Xe/CT CBF) on patients with SAH. Xe/CT were performed before and after acetazolamide loading within 10 days (early) and around one month (late) after the onset of SAH.

Cerebrovascular reserve capacities were disturbed in all patients with SAH in the early stage. Cerebrovascular reserve capacity recovered on the late stage. Hyperperfusion was noted in patient who showed symptomatic vasospasm, and the area of hyperperfusion (luxury perfusion area) revealed as an infarcted area on 3 months after the onset of SAH.

SAH itself has some role for disturbing the cerebral hemodynamic conditions.

16 CEREBRAL HEMODYNAMICS AND OXYGEN METABOLISM DURING AND AFTER DELAYED VASOSPASM

A. Hino, S. Taketomo, S. Ueda, N. Mizukawa, Y. Imahori, H. Tenjin, K. Hirakawa. Department of Neurosurgery, Saiseikai Kyoto-Fu Hospital and Kyoto Prefectural University of Medicine, Kyoto, Japan, Tokyo Medical and Dental University, Tokyo, Japan

We have conducted positron emission tomography(PET) to study cerebral hemodynamics and oxygen metabolism in postoperative patients with SAH. We reported that the patients had a decreased arterial oxygen content(CaO_2) due to postoperative hemodilution, impairement of regional perfusion due to cerebral vasospasm, and global metabolic supression of unknown origin during the period of delayed vasospasm (Stroke 20,1989). This study extends the previous report through a larger sample and the follow-up PET measurements. We measured CBF, oxygen metabolic rate($CMRO_2$) and extraction fraction(OEF), and cerebral blood volume(CBV) in 21 postoperative patients within 3 weeks and after 4 weeks of SAH. During the period of vasospasm, reductions in both the $CMRO_2$ and $CBF \times CaO_2$ (tissue oxygen supply) were seen, despite an increased CBF, in the apparently normal cortex, where CBV remained within normal limit and OEF increased according to the reduction in $CBF \times CaO_2$. This suggests a direct global metabolic supression by SAH, not an impairment of cerebral perfusion, which may also play a role in the developement of delayed neurological deficits. Postoperative managements should be focused to obtain not the optimal CBF value but the best balance of CBF, OEF and CaO_2 for the maximum $CMRO_2$ value, which most correlated with the patients' outcome

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

17 MAGNETIC RESONANCE ANGIOGRAPHY OF THE CEREBRAL VASOSPASM IN PRIMATES. H. Kobayashi, T. Tsuji, T. Kodera, Y. Arai, Y. Handa, T. Kubota
Department of Neurosurgery, Fukui Medical School, Fukui, Japan

The study was designed to assess cerebral vasospasm by both magnetic resonance(MR) and conventional X-ray angiography in primates.

Seven Japanese monkeys weighing from 8 to 11kg were used in this study. MR angiography was carried out on a 1.5 T GE Signa Advantage. After control MR and X-ray angiography, a right frontotemporal craniotomy was carried out and clot was placed over major cerebral arteries on Day 0. On Day 7, MR and X-ray angiography were performed twice, before and after administration of acetazolamide(Diamox 500mg i.p.).

There was no significant difference in physiological parameters between 1st, 2nd and 3rd angiography. The diameter of middle cerebral artery(MCA) in X-ray angiograms was 55.2 ± 2.8% on the right side, whereas that on the left side was 72.2 ± 2.5%($p<0.05$). There was no significant difference in the caliber of MCA between pre and postDiamox injection in X-ray angiograms. In MR angiography, the arteries on the clot side were more spastic than those on the other side. The postDiamox MR an giography showed a dramatic enhanced vasodilatation response to Diamox in both peripheral and proximal spastic arteries.

MR angiography is a promising technique to observe cerebral vasospasm but does not show the real size of the artery.

19 DOES VASOSPASM ALONE CAUSE DIND AFTER SAH ?
K. Kamiya, N. Yamashita, N. Sugiyama, M. Ono, H. Nagai
Department of Neurosurgery, Nagoya City University, Nagoya, JAPAN

Delayed ischemic neurological deficits(DIND) secondary to SAH are well documented but its causes are still uncertain yet. We have concentrated to study the hemodynamics , electrical activity and ionic homeostasis in the acute stage of SAH. These research suggested us following results.

1) Ischemic pattern after SAH is quite resemble to a recirculation model of forebrain ischemia. A definite difference is high ICP during recirculation period.

2) Brain edema in the acute stage of SAH is gray matter dominant.

3) Vasoreactivity(autoregulation and CO_2 reactivity) after SAH is impaired.

4) MCA occlusion after SAH suppressed cortical electrical activity and its pathway much more than ordinary MCA occlusion.

5) SAH increased extracellular K^+ and decreased Ca^{2+} as well as ordinary ischemia but these ionic failure were continued even after CBF returned to the level of control.

These results indicate that cerebral tolerance for ischemia has changed by an attack of SAH. Nowadays, pathology of SAH has been concentrated only to the vessels involved by vasospasm. We would like to stress that we must investigate vulnerable tissue for SAH in the brain itself, for example, hippocampus which is easily involved by transient ischemia as delayed neuronal death.

18 ALTERATIONS OF BASILAR ARTERY FLOW AND CEREBRAL MICROCIRCULATION FOLLOWING EXPERIMENTAL SAH
K. Ungersböck, A. Heimann, O. Kempski. Department of Neurosurgery and Institute of Neurosurgical Pathophysiology, University of Mainz, Mainz, Germany

The aim of this study was to investigate the alterations of cerebral macro- and microcirculation in the acute and chronic stage after SAH.

SAH was induced in rabbits by intracisternal injection of blood (0,5 ml/kg BW) over a period of 30 s during ketanest anesthesia. Control animals received mock CSF. Flow velocity in the basilar artery was recorded by ultrasound Doppler. Cerebral microcirculation was measured by laser Doppler flowmetry over the parietal cortex. Intracranial pressure, blood pressure and blood gas analysis were monitored. TCD was performed daily and microcirculation measurement repeated by day 5.

Results: Flow velocity (V) in the basilar artery decreased during blood injection and a waveform typically for intracranial circulatory arrest occured in both groups. In SAH animals this event was followed by a significantly decreased basilar flow velocity which lasted over the whole observation time (V mean 11,1±2,6 cm/s one hour after SAH versus 17,6±5,2 cm/s starting level). In control animals the initial drop of basilar flow velocity was followed by an immediate short hyperperfusion. After 5 min basilar flow velocity decreased moderately as compared to the starting level, and after 30 min the initial values were restored in the control group. In contrast the cerebral microcirculation in the supratentorial region was only transiently affected with early hyperperfusion in both groups. After 5 min no significant alteration was found compared to baseline values of 50.5 ±20.3 r.U. The intracisternal fluid injection caused in sudden rise of intracranial pressure which was significantly higher and longer in the SAH group . During the following 5 days in the SAH group a significant increase of basilar flow velocity was observed (28,2±5,0 cm/s on day 5 compared to 17,6±5,2 on day 1), with no change in the control group. After 5 days the cerebral micro-circulation in ketanest anesthesia showed no significant alteration compared to day one despite evident vasospasm in the basilar artery.

Conclusion: The sudden rise of ICP after experimental SAH produces transient impairment of cerebral perfusion pressure with alteration of the microcirculation in the acute stage after SAH. Basilar artery flow velocity is affected over a longer period, and is more sensitive for investigation of vasospasm than the cerebral microcirculation.

20 STATE OF ISCHEMIC VULNERABILITY OF BRAIN DURING CHRONIC CEREBRAL VASOSPASM IN PRIMATES. Y. Handa, Te. Kubota, H. Takeuchi, H. Kobayashi, H. Ishii, T. Kubota.
Department of Neurosurgery, Fukui Medical School, Fukui, Japan

The present study was designed to study the state of ischemic vulnerability during the chronic cerebral vasospasm, by evaluating how changes in perfusion pressure affect on the cerebral blood flow (CBF), energy metabolism, and electrical function of the brain in conjunction with the ischemic thresholds.

Thirty monkeys were used. In all the animals, SAH was produced by introduction of a blood clot around the right middle cerebral artery (MCA). After second angiography on Day 7 following SAH, changes in CBF at the bilateral parietal cortex and central conduction times (CAT) were recorded during graded alteration of mean arterial blood pressure (MABP) from 40 to 180 mmHg. To evaluate the state of energy metabolism, changes in phosphorus spectrum, by means of an *in vivo* phosphorus magnetic resonance spectroscopy, in the bilateral parietal cortex were recorded during graded alteration of MABP.

Angiograms revealed the reduction of vessel caliber of approximately 50 % in the right MCA on Day 7. The changes in mean CBF in the left non-spasm side revealed the preservation of autoregulation at MABP from 60 to 160 mmHg. The mean CBF in the right spasm side changed in parallel with changes in the MABP from 40 to 180 mmHg, indicating the abolition of autoregulation. In the spasm side, the hypotension at 60 mmHg caused a decrease in CBF (20 ml/100 gm/min) leading to a significant ($p < 0.05$) reduction in phosphocreatine and an increase in inorganic phosphate in phosphorus spectrum, and the hypotension at MABP of 40 mmHg reduced CBF to 15 ml/100 gm/min causing a significant reduction in the tissue ATP level and a marked prolongation in CCT.

The results indicate that during chronic vasospasm, changes in cerebral energy metabolism are coupled with changes in CBF in the state of impaired autoregulation. The state of the energy metabolism exists at the critical level for ischemia in which high-energy phosphorus metabolites become markedly depleted, and may be easy to cause the synaptic failure of neuronal cells.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

21 INFLUENCES OF VASOSPASMS ON THE r-CBF AND PREDICTION OF PROGNOSIS AFTER SUBARACHNOIDAL HEMORRHAGE

T.Fukuda,M.Hasue,H.Ito
Department of Neurosurgery,Tokyo Medical College

It is well known that the cerebral blood blow (CBF) decreases significantly in the ischemic brain after subarachnoid hemorrhage (SAH) caused by reputured aneurysm. However the relationships between regional CBF and its prognosis in relation to vasospasm is unsolved. r-CBF was measured at early (within 4 days after SAH)and delayed (7th day)stages after SAH in 113 cases.

113 Xe two-compartment analysis and I-IMP SPECT was employed to estimate r-CBF.

Before the time of angiographically recognizable vasospasm changes, 80 out of 113 cases demonstrated remarkably decreaed r-CBF in the acute stages after SAH. Cases of decreased r-CBF with less than 50ml/100g/min on the Xenon analysis (standard range 80 ± 9.9ml)and less than 30 by the I-IMP SPECT reference sample method (standard range 42.4 ± 6.0) showed poor prognosis. In 70% of these poor prognostic cases, intracerebral delayed infarction by ischemia occurred in the following subacute stages. As a result, 47% of cases of delayed cerebral ischemic changes were severely handicapped. In contrast, only 15% of cases of moderately decreased CBF showed cerebral ischemia after treatment, and 80% of cases in this group had good results.

The moderately decreased group had better outcome than the severely decreased r-CBF groups even though clinical or CT grading in SAH showed similar results in the acute stages. There was no significant difference between the two groups in terms of the severity of vasospasm on the angiographical findings in the subacute stage. We conclude that a marked decrease in r-CBF in the acute stage after SAH may be a significant risk factor for the development of delayed cerebral ischemia as well as cerebral vasospasm in the subacute stage.

SESSION C
Smooth Muscle, Calcium, Protein Kinase C and Vasospasm

22 CALPAIN ACTIVATION IN THE RABBIT BASILAR ARTERY AFTER SUBARACHNOID HEMORRHAGE P.L. Foley, P. Vanderklish*, G. Lynch*, N.F. Kassell, K.S. Lee. Department of Neurosurgery, Univ. of Virginia, Charlottesville, VA 22908, *CNLM, Univ. of California, Irvine, CA 92717

Vasoconstriction due to increased intracellular calcium levels in smooth muscle cells is believed to be a key event in the development of vasospasm after subarachnoid hemorrhage (SAH). Calcium-activated proteolysis via calpain may contribute to vasospasm by impairing the function of key proteins regulating smooth muscle tone. The present studies examined this issue by measuring calpain levels in the rabbit basilar artery following SAH. Two to four days following experimental SAH, basilar arteries were removed, thoroughly flushed with cold homogenization buffer to remove all blood, dissected free from the brainstem, and placed into 100µl of cold buffer. The tissue was subsequently homogenized using teflon tissue grinders. Western blot analyses were performed using two antibodies, one for calpain, and another for spectrin (a cytoskeletal protein which is a preferred substrate of calpain).

Vessels from normal rabbits exhibited high levels of native calpain and native spectrin. Vessels removed 2 to 4 days after SAH showed significant decreases in the levels of native calpain and native spectrin, and an elevation in spectrin breakdown products. The reduction in levels of native calpain suggests that autoproteolytic activation of this protease had occured. In addition, the sizes of the spectrin breakdown products were typical of those observed following calpain proteolysis. These findings indicate that calpain activation occurs following SAH, and that this mechanism could contribute to the pathophysiology of vasospasm.

23 **THE TIME COURSE OF MYOSIN LIGHT CHAIN PHOSPHORYLATION IN VASOSPASM.** T. Harada, M. Seto, Y. Sasaki, S. London, Z. Luo, M.R. Mayberg, *Department of Neurological Surgery, University of Washington, Seattle, WA USA and Biochemical Research Laboratory, Asahi Chemical Industry Co., Miyazaki, JPN*

In most agonist-mediated vascular smooth muscle cell (SMC) contraction, intracellular calcium and calmodulin mediate the phosphorylation of 20 kD myosin light chain (MLC_{20}), which promotes contactile force generation through actin-myosin ATPase. Whole blood in a silastic cuff was applied to femoral arteries in 54 rats; the contralateral artery served as matched control. At 2,3,4,5,7 and 10 days after application, arteries were removed, washed free of blood and immediately frozen. Total MLC_{20} and MLC_{20} phosphorylation (non- ,mono- and di-phosphorylated forms) were measured by immunoblotting and polyacrylamide gel electrophoresis, respectively.

In control arteries, tissue levels of MLC_{20} (0.8 µg/mg) and the ratio of mono- to non-phosphorylated MLC_{20} (18%-23%) were constant at all time periods. In arteries exposed to blood, MLC_{20} tissue levels were comparable to controls on days2 through 5, after which there was a significant decrease to less than 10% of control values by day 10. MLC_{20} phosphorylation increased dramatically (30%-38%) between days 3 and 5 after blood exposure, including di-phosphorylated forms (1%-3.6%). At 7 and 10 days, however, phosphorylated MLC_{20} was undetectable due to the marked decrease in tissue levels. These data suggest that contractile force-generating processes are prominent in the early stages (days 3-5) of arterial narrowing after SAH; later stages are associated with loss of MLC_{20} and possible persistence of arterial narrowing by other mechanisms.

24 MODIFICATION OF CONTRACTION-RELATED PROTEINS IN RABBIT BASILAR ARTERY AFTER SUBARACHNOID HEMORRHAGE.

K. Takenaka, Y. Goto, N.F. Kassell, K.S. Lee. Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia, 22908

The pathophysiology of vasospasm was studied by measuring changes in smooth muscle regulatory proteins following experimental subarachnoid hemorrhage (SAH). SAH was induced in male New Zealand white rabbits by a single injection of autologous arterial blood. Western blot techniques were used to measure the content of caldesmon, myosin light chain, and tropomyosin in control animals and animals subjected to SAH (day 2). Immunoblotting was performed after transfer of proteins onto nitrocellulose sheets from SDS-polyacrylamide gels. Immunoreactivity against low molecular weight caldesmon and myosin light chain was significantly reduced in animals subjected to SAH. In contrast, the levels of high molecular weight caldesmon and tropomyosin were not changed significantly. These data suggest that SAH induces alterations in certain smooth muscle proteins in the basilar artery. The decreases in these proteins could contribute to the pathogenesis of delayed vasospasm after subarachnoid hemorrhage.

25 EFFECT OF 5-HYDROXYTRYPTAMINE ON ORGANELLE TRANSPORT IN CULTURED VASCULAR SMOOTH MUSCLE CELLS Y. Tanabe, S. Fujii, Y. Takanashi, K. Fujitsu, T. Kawakami, T. Takenaka, and I. Yamamoto. Department of Neurosurgery and Department of Physiology, Yokohama City University, Yokohama, Japan

Histological studies of cerebral arteries in vasospasm have well shown various changes of organelles in smooth muscle cells. To investigate the process of these changes we observed organelle transport in cultured smooth muscle cells of rabbit basilar artery with a computer assisted video enhanced microscopic system. These organelles moved along microtubules in both centrifugal and centripetal directions. The instantaneous velocities of organelles in the centrifugal and centripetal directions were 0.84±0.36μm/sec and 0.86±0.48μm/sec,respectively. The transported organelles studied with fluorescent staining mainly consisted of lysosomes(67.5%) and mitochondria(29.0%). Application of 5-hydroxytryptamine(5-HT) resulted in transient extension of organelle transport in both directions. These results suggest that 5-HT regulates organelle transport in cultured vascular smooth muscle cells and this response is relevant to changes of organelles in vasospasm.

26 DECREASED SENSITIVITY OF INTRACELLULAR CALCIUM SIGNAL AND FORCE DEVELOPMENT TO EXTRACELLULAR CALCIUM IN THE SPASTIC CEREBRAL ARTERIES P.Kim, Y.Yoshimoto, T.Sasaki, K.Takakura, M.Iino, Y.Nonomura Departments of Neurosurgery and Pharmacology, University of Tokyo, Tokyo

To investigate if regulation of calcium is altered in the smooth muscle of the cerebral artery during vasospasm, intracellular calcium levels ($[Ca]_i$) of the isolated basilar artery strips were measured using fluorescent dye Fura 2. Double hemorrhage canine model was used and spasm of the basilar artery was confirmed angiographically on days 3 and 7. $[Ca]_i$ signal and development of tension were monitored simultaneously, as the extracellular calcium level ($[Ca]_o$) was altered stepwise (PCa7 to 2). $[Ca]_i$ signal rose as $[Ca]_o$ increased beyond PCa5; the rise was smaller in the spastic arteries than in the control. The threshold (PCa5) was comparable. Tension development in response to the rise in $[Ca]_o$ was markedly suppressed in the spastic arteries, with the threshold shifted rightward. In the spastic arteries, intensity of fluorescence after identical loading condition was smaller, and leak of the dye was greater than in the control group, leading into distortion of "mirror image" of the emission signals excited at 340nm and 380nm. The resting $[Ca]_i$, as calculated following the formula by Grynkiewicz et al, was not elevated in the spastic arteries.

The results indicate that the spastic cerebral artery does not have increased sensitivity to extracellular calcium, both in terms of $[Ca]_i$ changes and contractility. The impaired loading and greater leakage of the dye suggests affected viability of the smooth muscles in the condition.

27 TIME COURSE AND SIGNIFICANCE OF METABOLIC FAILURE AND TROPHIC CHANGES IN THE CEREBRAL ARTERY IN VASOSPASM Y.Yoshimoto, P.Kim, T.Sasaki,K.Takakura Dept.of Neurosurgery, University of Tokyo, Tokyo

To investigate pathogenetic relevance of the metabolic failure observed in the cerebral vasculature during chronic vasospasm, the course of alterations in the arterial high energy phosphate content was studied. Double hemorrhage canine model was used and constriction of the basilar artery was measured angiographically on day 3, 5, 7, 14 in separate groups. Contents of ATP, ADP, AMP, GTP, GDP, creatine phosphate (Cr-P) and creatine (Cr) in the artery were assayed using high performance liquid chromatography. A time-dependent development of angiographical spasm was confirmed; a mild vasospasm was seen on day 3, progressed on day 5, it remained comparably severe on day 7 and resolved partially on day 14. Contents of high energy phosphates (ATP, GTP, Cr-P) diminished rapidly in the course; a significant reduction was seen on day 3 and ATP and Cr-P decreased further on day 5 and day 7. Decrement of GTP was completed in the early phase; a significant reduction took place by day 3 with no progression thereafter. No recovery in the high energy phosphates was observed on day 14, despite partial resolution of vasospasm. Values of total adenylate content (AMP+ADP+ATP) and total creatine content (Cr+Cr-P) diminished markedly over the course. These results indicate that the metabolic failure and trophic changes in the arterial wall take place in close correlation with development/progression of the narrowing of the artery, and suggest a significant causal conjunction with the pathogenesis of vasospasm.

28 INVOLVEMENT OF CALCIUM BINDING PROTEINS IN THE DEVELOPMENT OF ARTERIAL SPASM M. Doi[1], B.G. Allen[3], M.P. Walsh[2], H.Kasuya[3], B.K.A. Weir[1], D.A. Cook[1] Department of Pharmacology, University of Alberta, Edmonton, Alberta, CANADA T6G 2H7[1], Department of Medical Biochemistry, University of Calgary, Calgary, Alberta[2] and Department of Neurosurgery, University of Chicago, Chicago, Illinois[3].

The sustained increases in cytosolic calcium which accompany the development of vasospasm may be associated with dysfunction of calmodulin or calponin, proteins which bind calcium and are involved in smooth muscle contraction. To investigate this hypothesis, we have examined the effects of the calmodulin inhibitor trifluoperazine (TFP) on the contractile properties of rings of cerebral artery obtained from the single haemorrhage canine model. Preparations from spastic arteries were significantly more sensitive to TFP than were preparations from control arteries. suggesting that there is alteration of calmodulin function under these circumstances. Smooth muscle contraction is controlled also by calponin, a protein which inhibits actin-myosin interaction and whose phosphorylation by protein kinase C or Ca^{2+}-calmodulin dependent kinase II attenuates its action. It is thus possible that this protein also becomes dysfunctional in vasospasm, and in order to investigate this phenomenon, we have examined calponin levels in control and in spastic vessels using a model of vasospasm in the rat femoral artery. Calponin was determined by non-equilibrium pH gradient electrophoresis (NEPHGE). The results cannot exclude a role for calponin as well as calmodulin in vasospasm.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

29 CONTRACTILE FORCE REGULATION IN CHRONIC CEREBRAL VASOSPASM W.E. Butler, J.W. Peterson, N.T. Zervas, S. Chase, M. Kaoutzanis, M. Yokota, K.G. Morgan. Cardio-Vascular Division, Beth Israel Hospital, Program in Smooth Muscle Research, Harvard Medical School, Boston, Massachusetts

In the Ca^{2+}- dependent pathway of smooth muscle contraction, increased cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) leads sequentially to increased Ca^{2+}-calmodulin binding, increased myosin light chain kinase (MLCK) activity, increased myosin light chain (MLC) phosphorylation, and increased force generation. The intracellular mechanisms of arterial narrowing in cerebral vasospasm are unknown. Thus, contractile force, $[Ca^{2+}]i$, and MLC phosphorylation were measured in double subarachnoid hemorrhage model of cerebral vasospasm. Force and $[Ca^{2+}]i$ (measured with the luminescent Ca^{2+} indicator aequorin) were measured simultaneously *in vitro*. Intrinsic tone, defined as the basal tension at 37 degrees centrigrade minus the tension at 0 degrees, was significantly greater in vasospastic than control vessel segments (5.2 kN/m^2 vs 2.0 kN/m^2, $p< .05$). Furthermore, vasospastic segments had increased basal $[Ca^{2+}]i$ (398 nM vs 258 nM, $p<.025$). In parallel experiments, upon sacrifice vasospastic vessels were immediately excised and quick frozen. Subsequently, 2-D gel electrophoresis was used to measure percent MLC phosphorylation. Vasospastic vessels had increased MLC phosphorylation (37% vs 2%, $p<.05$), suggesting a causal link between vasospasm's increased basal $[Ca^{2+}]i$ and increased intrinsic tone. Thus, chronic cerebral vasospasm must involve increased $[Ca^{2+}]i$, increased MLCK activity, increased MLC phosphorylation, and increased intrinsic force generation.

30 Alterations of protein kinase C (PKC) activity following subarachnoid hemorrhage. T. Matsui, (*) Y. Takuwa, T. Nagafuji, H. Kaizu, T. Asano. Department of Neurosurgery, Saitama Medical Center/School, Saitama, Japan. (*)Department of Cardio-vascular Biology, Faculty of Medicine, University of Tokyo, Tokyo, Japan.

We have already reported that protein kinase C (PKC) activation participates in the development of chronic vasospasm (VS) following subarachnoid hemorrhage (SAH). The present study was undertaken to examine lipid metabolism contributing to the increase in 1,2 diacylglycerol (DAG) contents in the spastic basilar artery (BA), and to compare 20 kDa myosin light chain (MLC) phosphorylation and PKC activity of BA on Days 4, 7 and 14 with those of control BA, respectively. Time coursed analysis of alterations in PKC isoforms was also made by Western blots. The significantly higher turnover of PC and PE might be a source of the increase in DAG contents of spastic BA. No significant increase in MLC phosphorylation was obtained but PKC was down-regulated on Days 4 and 7. Regarding PKC isoforms, α and ζ were down regulated and ε was unaltered during the course of VS. On Day 14, pattern of PKC isoforms tended to be that of control BA. The evidence of PKC down-regulation leads to conclusion that PKC activation has occurred during the course of SAH.

31 PROTEIN KINASE C MODULATES INCREASED CEREBROVASCULAR REACTIVITY CAUSED BY ACTIVATED PLATELETS. I. Laher, P. Germann, J. Bevan, University of Vermont, Department of Pharmacology, Burlington, VT 05405-0068

Hemolysis of red blood cells and aggregation of platelets is associated with intense vasospasm during the acute phase of subarachnoid hemorrhage. We tested the hypothesis that the enhanced vascular reactivity caused by aggregated platelets is mediated by protein kinase C (PKC). The sensitivity of the rabbit basilar artery to thrombin (ED_{50} 4 ± 0.1u/ml) was increased (ED_{50} 1 ± 0.3u/ml) in segments exposed to collagen-activated human platelets (8 x 10^8cells/ml). In artery segments pretreated with staurosporine (10nM, 40 min), a relatively selective inhibitor of PKC, the ED_{50} for thrombin in the presence of activated platelets (ED_{50} 3.5 ± 0.2u/ml) was not different from control. Staurosporine also blunted the increase in the maximal response caused by activated platelets. The characteristics of the dose-response curve to thrombin were not altered by removal of the endothelium but the ability of activated platelets to sensitize responses to thrombin was significantly enhanced. We conclude that amplification of constrictor responses to thrombin caused by platelet derived products may be due to activation of PKC. Our results also suggest that the endothelium may play a protective role in the acute phase of SAH by reducing the extent of vascular hyperresponsiveness caused by platelet derived mediators. Supported by USPHS HL 32383 and The Ray and Ildah Totman Medical Research Fund

32 IMMUNOHISTOCHEMICAL STUDY OF PKC IN DOG AFTER SUBARACHNOID HEMORRHAGE M. Yokota, E. Tani, Y. Maeda, I. Yamaura, N. Minami, J.W. Peterson. Department of Neurosurgery, Hyogo College of Medicine, Hyogo, Japan and Neurosurgical Service, Massachusetts General Hospital, Boston, MA

PKC regulates diverse cellular functions including smooth muscle contraction. The effects of SAH on PKC immunoreactivities (IR) were studied in canine brain and basilar artery (BA). SAH was produced by two-hemorrhage method (3 days apart). Animals were perfused 3 days (Day 3) or 6 days (Day 6) after 1st SAH. Pons (PO), hippocampus (HC), cerebellum (CB) and BA were stained with PKCα, ß and γ antibodies (Ab). In the normal PO, PKCα Ab stained neurons in the pontine nuclei and glial cell. In normal HC, PKCα Ab stained pyramidal cells in CA1-4 stronger than PKCß and γ and Ab. In normal CB, PKCγ Ab stained Purkinje cells; PKCß Ab stained the granule cells ; and PKCα Ab stained the Purkinje and glial cells. In normal BA, only PKCα IR was found in smooth muscle cells. In CB, IR of PKC showed no change after SAH. PKCα IR astrocytes emerged in the PO and HC adjacent to the clot, and IR of glial process in the PO became prominent on Day 6. PKCα IR did not alter in the BA on Day 3 but showed patchy distribution on Day 6, similar to that produced by phorbol ester application *in vitro*. These results suggest that the alteration of PKCα activity may play a role in the pathogenesis of vasospasm and gliosis after SAH.

33 PROLONGED ACTIVATION OF PROTEIN KINASE C IN OXYHAEMOGLOBIN-INDUCED VASOCONSTRICTION IN CANINE BASILAR ARTERY D.A. Cook, T. Luong, M. Doi, B. Vollrath. Department of Pharmacology, University of Alberta, Edmonton, Alberta, T6G 2H7 CANADA

The sustained increases in diacylglycerol (DAG) in spastic vessels may arise from breakdown of phosphatidylcholine (PC) which is either receptor mediated or arises from increased intracellular Ca^{2+} which activates phospholipase D, with resultant PC hydrolysis. DAG is known to activate protein kinase C (PKC) and this may be responsible for the sustained phase of the vasoconstriction. We have thus examined the effects of inhibitors of PKC on the response of isolated rings of canine cerebral artery to oxyhaemoglobin (O_2Hb). Pretreatment with staurosporin or H7 reduced the contraction to O_2Hb by about 60%, and the new agent chelerythrine, which is highly selective for PKC, had similar effects. Staurosporin and H7 produced a dose-dependent reduction in the response to O_2Hb when given at the peak of the contraction, although they also had some effects on the responses to potassium chloride, suggesting either that these agents may have some action on myosin light-chain kinase as well as on PKC, or that activation of an isoform of PKC may be involved in the sustained response to potassium chloride. We conclude that prolonged activation of PKC may occur during the tonic phase of the response of cerebrovascular smooth muscle to O_2Hb, and, since O_2Hb may be the causative agent in vasospasm, these results are consistent with other data which supports a role for the activation of PKC in this condition.

34 PROTEIN KINASE C AND INTRACELLULAR CALCIUM IN OXYHEMOGLOBIN-TREATED SMOOTH-MUSCLE CELLS Y. Takanashi, S. Fujii, K. Fujitsu, I. Yamamoto, B. Weir, D. Cook. Department of Neurosurgery, Yokohama City University, Yokohama, University of Chicago, Chicago, Illinois, University of Alberta, Edmonton, Alberta

Oxyhemoglobin is a strong candidate for mediator of cerebral vasospasm that follows subarachnoid hemorrhage. To observe the effect of oxyhemoglobin for the smooth-muscle cells, protein kinase C activity and intracellular free calcium concentration were examined. During culture, smooth-muscle cells obtained from rabbit basilar arteries were measured for protein kinase C activity by Western blot analysis. Protein Kinase C activity of the cells did not increase for up to 6 days after exposure to oxyhemoglobin. Intracellular calcium concentration of smooth-muscle cells obtained from monkey middle cerebral arteries was examined for up to 7 days after exposure to oxyhemoglobin. Intracellular calcium concentrations were significantly elevated during application of oxyhemoglobin. The exact role of protein kinase C is still unclear, while disruption of intracellular calcium regulation may have crucial roles in the cell damage during cerebral vasospasm.

35 ACTIVATION OF PROTEIN KINASE C INHIBITS OUTWARD POTASSIUM CURRENT IN CULTURED ENDOTHELIAL CELLS. H. Zhang, E.E. Daniel and B. Weir. Department of Biomedical Sciences, McMaster University, Hamilton, Ontario and Neurosurgery, The University of Chicago, Chicago, illinois.

A large inward and a small outward potassium currents were obtained by whole-cell patch-clamp from cultured bovine pulmonary endothelial cells. Activation of protein kinase C by phorbol myristoyl acetate (PMA) and phorbol 12,13-dibutyrate (PDBu) dose-dependently (0.3-10 uM) depressed the outward current but without effects on the inward current. The inactive analog phorbol 12-monomyristate (PMM) was devoid of any effects at same concentrations. The inhibitory actions of PMA and PDBu were blocked by kinase inhibitor H-7 (10 uM). Cyclopiazonic acid (CPA,3-20 uM), an inhibitor of the sarcoplasmic reticulum calcium pump, and LP-805 (1-100 uM), a novel potassium channel opener, increased the outward conductance which was sensitive to TEA (1-10 mM), 4-AP (5 mM) and charybdotoxin (100 nM). PMA and PDBu, but not PMM, reduced the outward conductance induced by CPA and LP-805. Activation of protein kinase C may produce a negitive feedback control to the influx of calcium into the endothelial cells. The mechanism for modulating potassium conductance by phorbol esters in endothelial cells needs to be clarified. Supported by MRC Canada and NIH R01 NS25957-03.

SESSION D
Hemoglobin, Free Radicals and Vasospasm

36 PENETRATION OF HEMOGLOBIN INTO THE BASILAR ARTERIAL WALL AFTER SUBARACHNOID HEMORRHAGE P.L. Foley, N.F. Kassell, K. Takenaka, K.S.Lee, Department of Neurosurgery, University of Virginia, Charlottesville, VA 22908

Hemoglobin (Hb) is postulated to participate in the pathogenesis of cerebral vasospasm. This study examined the extent to which Hb penetrates the basilar arterial wall after subarachnoid hemorrhage(SAH). Using 1-D PAGE and transblotting analyses, two anti-Hb antibodies were first tested to establish their reactivity with rabbit Hb. Basilar arteries were then obtained from rabbits subjected to SAH. Arteries were removed two or four days following SAH and sectioned transversely with a cryostat. The distribution of Hb antibodies was examined in the tissue sections using indirect immunofluorescence. Vessels taken from animals sacrificed 2 days after SAH exhibited Hb-immunofluorescence primarily in the adventitia and smooth muscle layers, with limited penetration to the endothelium. Vessels from animals sacrificed 4 days after SAH showed immunofluorescence in all layers of the vessel wall. The extent of Hb penetration that occurred in the vessels correlated with the degree of vasoconstriction following SAH.

These observations demonstrate that Hb reaches both smooth muscle and endothelial cells after SAH. A direct effect of Hb on the endothelium may contribute to SAH-induced vasospasm by altering the ability of endothelial cells to modulate vascular tone.

37 CYTOTOXICITY OF CULTURED ENDOTHELIAL CELLS INDUCED BY OXYHEMOGLOBIN OR BLOODY CSF P.L. Foley, K. Takenaka, N.F. Kassell, K.S. Lee. Department of Neurosurgery, University of Virginia, Charlottesville, VA 22908

The effects of oxyhemoglobin (oxyHb) and bloody cerebrospinal fluid on endothelial cells were studied to ascertain their possible contribution to vascular pathophysiology, using cultured endothelial cells from bovine carotid or middle cerebral artery. Prolonged incubation (up to 15 days) with 10μM oxyHB resulted in a gradual decrease in cell density while treatment with a higher concentration (100μM) resulted in reduced cell density within 3 days. Changes in both cell density and morphology were time- and dose-dependent. Superoxide dismutase, a free radical scavenger, provided partial protection against the cytotoxic effects of oxyHb. Treatment with oxyHb also elicited an increase in the release of arachidonic acid in a time- and dose-dependent manner. Bromophenacyl bromide, an inhibitor of phospholipase A_2, and EGTA, a calcium chelator, inhibited the effects of oxyHb on arachidonic acid release and cellular viability. CSF preincubated with blood for 1 to 7 days also promoted cytotoxicity in a time dependent manner, which correlated with the increase in oxyHb concentration in these solutions.

These results demonstrate that oxyHb exerts a cytotoxic effect on cultured endothelial cells and that this effect is associated with increased release of arachidonic acid. The data also indicate that calcium, phospholipase A_2 and free radicals critically participate in the pathogenesis of endothelial cell damage. Bloody CSF exerts a similar cytotoxic effect which is likely to be related to release of endogenous oxyHb. These effects may play a role in the pathogenesis of vasospasm in which endothelial cells are damaged after SAH.

38 EXPERIMENTAL VASOSPASM USING CULTURED SMOOTH MUSCLE CELLS - CORRELATION BETWEEN PROLONGED CONTRACTION AND PROTEIN PHOSPHATASE S. Fujii, Y. Tanabe, Y. Takanashi, K. Fujitsu, K. Hirata, I. Yamamoto. Department of Neurosurgery, Yokohama City University, Yokohama, Japan

We have already reported that smooth muscle cells(SMCs) showed progressive contraction and various ultrastructural changes when cultured in the medium with oxyhemoglobin(OxyHb) and this OxyHb induced contraction was not associated with a proportional increase in cytosolic free calcium $[Ca^{2+}]i$. For invesigating these experimental results, we examined a correlation between prolonged contraction of SMCs and protein phosphtase, a key enzyme of SMC relaxation. With the usage of okadaic acid, a newly developed protein phosphatase inhibitor, prolonged contraction was seen, but no increase of $[Ca^{2+}]i$ was identified. We also studied an augmenting effect of OxyHb for the okadaic acid induced contraction, however, no such effect was demonstrated in this experiment. Further examination was needed for analysis of the mechanisms of prolonged contraction without increase of $[Ca^{2+}]i$.

39 DIFFERENTIAL EFFECTS OF OXYHEMOGLOBIN AND HEMOLYSATE ON BASILAR ARTERY *IN VITRO*
T. Aoki, K.S. Lee, N.F. Kassell. Department of Neurosurgery, University of Virginia, Charlottesville, VA 22908

Many studies have implicated oxyhemoglobin (oxyHb) in the development of vasoconstriction after subarachnoid hemorrhage (SAH). Conflicting evidence exists, however, regarding the direct vasoconstrictive effects of oxyHb. Using an *in vitro* preparation of the rabbit basilar artery, we compared the effects of several concentrations of oxyHb-alone with the same concentrations of oxyHb derived from lysed erythrocytes. Washed erythrocytes were lysed by freezing and thawing, and the supernatant separated from red blood cell ghosts by centrifugation. OxyHb content of the supernatant was determined by scanning absorption spectrophotometry. Isometric tension measurement recordings using rabbit basilar arterial rings were performed while adding cumulative doses of either oxyHb or supernatant to the organ bath chambers.

At a concentration of 10^{-4}M, oxyHb-alone elicited a stronger constriction than an equal concentration of oxyHb in hemolysate. Increasing concentrations of oxyHb in supernatant progressively constricted the vessels. In contrast, concentrations greater than 10^{-4}M of oxyHb-alone induced a dilation of the vessels. These observations suggest that the vasoconstrictive effect of oxyHb-alone is limited at higher concentrations (>10^{-4}M). Other factors or cofactors released from lysed red blood cells may therefore be essential for induction of vasoconstriction after SAH.

40 **ANTI-OXIDANTS AND IRON CHELATING AGENTS IN CEREBRAL VASOSPASM.** T. Harada, Z. Luo, C. Gajdusek, S. London, M.R. Mayberg, *Department of Neurological Surgery, University of Washington, Seattle, WA USA*

Prior work in our laboratory showed that deferoxamine (an anti-oxidant and iron-chelating agent) effectively inhibited delayed arterial narrowing in a rat femoral artery model. To determine which of these mechanisms was operant in vasospasm, we compared deferoxamine to agents (ascorbic acid, U74389F [Upjohn]) with anti-oxidant but not iron-chelating capacity. In 40 rats, whole blood encased in a silastic cuff was applied to the right femoral artery; serum lacking erythrocytes was similarly applied to the left femoral artery as a matched control. In 20 rats, deferoxamine, ascorbic acid, U74389F, or pH-matched control vehicle were administered 3 times daily by intraperitoneal injection. In 20 rats, drugs or vehicle were directly mixed with blood or serum at the time of perivascular application. At 7 days, vessels were perfusion-fixed and luminal area determined by automated image-analysis.

Vehicle-treated arteries showed a 68% reduction in lumen area at 7 days after blood exposure. Intraperitoneal ascorbic acid and U74389F produced small (56% and 52% decrease in lumen area, respectively) but significant lessening in arterial narrowing ($P<0.05$). Perivascular application of all three drugs significantly inhibited arterial narrowing. These data suggest that mechanisms related to generation of cytotoxic free radicals may play an important role in cerebral vasospasm. In addition, the concentration of drugs in the perivascular thrombus is critical to their efficacy.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

41 EFFECT OF HISTIDINE, A FREE RADICAL SCAVENGER, ON SUBARACHNOID HEMORRHAGE-INDUCED VASOSPASM IN THE RABBIT

M. M. Fadel, P. L. Foley, N. F. Kassell, K. S. Lee
Department of Neurological Surgery, University of Virginia, Charlottesville, VA 22908

Damage due to free radical generation is thought to play a central role in the pathogenesis of cerebral vasospasm. The effect of a naturally-occurring free radical scavenger, L-Histidine (His), was examined in an experimental model of subarachnoid hemorrhage (SAH) -induced cerebral vasospasm. Forty-one rabbits were divided into the following groups: (1) *Control* (no SAH), n=10; (2) *SAH only*, n=10; (3) *SAH+Vehicle*, intravenous saline injections 4 times daily for 48 hours starting 20-30 minutes before SAH, n=6; (4) *SAH+Low Dose His*, 50mg/kg twice daily over the same time interval, n=7; (5) *SAH+High Dose His*, 100mg/kg four times daily for the same time period, n=8. The rabbits were perfusion-fixed 48 hours after SAH. The basilar artery was removed and processed for morphometric analysis.

A dose-dependent reduction in the amount of vaso-constriction was observed in the His-treated groups. Relative to the *SAH-only* group, the degree of vasospasm was attenuated by 28% in the *Low Dose* group and by 46% in the *High Dose* group. These effects were significant at the $p<0.05$ and $p<0.01$ levels, respectively (Student's t-test). These findings demonstrate that His can partially protect against SAH-induced vasospasm. The protective effect of His is postulated to be the result of its known ability to scavenge singlet oxygen and hydroxyl free radicals.

42 EXPERIMENTAL SAH: AN UNIFYING HYPOTHESIS ON BRAIN DAMAGE FOLLOWING THE HEMORRHAGE

F.Marzatico, P.Gaetani*, C.Café, R.Bellazzi*, S.Quaglini** and R.Rodriguez y Baena*
Institute of Pharmacology, * Dept.of Surgery, Neurosurgery, IRCCS Policlinico S.Matteo, **Dipartimento di Informatica e Sistemistica, University of Pavia, Italy

Recent studies have suggested that after SAH the reduction of cerebral metabolism may be independent on cerebral ischemia related to vasospasm: however, the neurochemical correlates of this peculiar situation are unclear. Authors have analyzed whether a correlation exists between time-dependent modifications of enzymatic lipid peroxidation ("ex vivo" release of LTC4) and anti-oxidant enzymatic systems (the cytoplasmatic Cu Zn SOD, the mitochondrial MnSOD and glutathione peroxidase = GSH-Px) in the brain compartment after experimental SAH induction in the rat. The release of the LTC4 is significantly enhanced at 1,6 and 48 hours after SAH induction; Cu-Zn SOD activity is significantly reduced at 6 and 48 hours after SAH induction; Mn-SOD activity is affected at 1,6 and 48 hours after SAH. GSH-Px activity is reduced only at 48 hours after SAH. The linear regression method allowed to verify any possible relationship among time-dependent modifications of the different parameters considered using

The regression LTC4 vs log (MnSOD) resulted highly significant ($p< 0.001$) with a negative coefficient for MnSOD and a correlation coefficient (Filliben) for residuals with normal distribution = 0.9289. The regression LTC4 vs. CuZn SOD did not show any significant result, while the regression LTC4 vs. GSH-Px gave a significant $p = 0.011$. These results suggested a significant correlation between the trend of MnSOD activity and LTC4 release, while results concerning GSH-Px and CuZn SOD activities may be considered less significant. If we assume that subarachnoid bleeding "per se'" may be the cause of significant changes in oxidative metabolism and the reduced consumption of O2, we may consider the enhanced release of LTC4 and the reduced MnSOD activity as an epiphenomenon of primary metabolic derangement caused by SAH. The marked impairment of MnSOD activity may contribute to favor the peroxidative damage, reflecting the inability to provide a complete defense from superoxide radicals in the mitochondrial compartment. The present results suggest an unifying hypothesis of brain damage following SAH and suggest a rationale for pharmacological treatment with anti-oxidant compounds for brain protection against detrimental effects of subarachnoid hemorrhage.

43 HUMAN RECOMBINANT SUPEROXIDE DISMUTASE PREVENTS CEREBRAL VASOSPASM IN A RABBIT SUBARACHNOID HEMORRHAGE MODEL

T. Shishido, R. Suzuki, L. Qian, Y. Niimi, H. Masaoka, K. Hirakawa. Department of Neurosurgery, Tokyo Medical and Dental University, Tokyo, Japan

To investigate the role of free radical reactions in the genesis of cerebral vasospasm, we used a free radical scavenger; human recombinant copper-zinc superoxide dismutase (h-r SOD) in a rabbit subarachnoid hemorrhage (SAH) model. **Method** Forty-five rabbits received intracisternal injection of 3ml saline (n=6), or 3ml autologous non-heparinised blood (n=39). They were divided into 4 groups as follows. 1) Saline-injected and no treatment (Control group, n=6); 2) Blood-injected and no treatment (SAH group, n=20); 3) SAH animals received intracisternal injections of 0.5 ml saline every 12 hours until 72 hours after the start of the experiment (Sham group, n=10); 4) SAH animals received intracisternal injections of 30,000 units of h-r SOD in 0.5 ml saline every 12 hours until 72 hours after the start of the experiment (SOD group, n=9). Serial vertebral angiograms were obtained prior to the intracisternal blood injection and at 1 hour, 1, 2, 4, 7, and 11 days after the intracisternal blood injection in each group. Diameter of the basilar artery was measured in each angiogram and compared to that of baseline angiogram in each rabbit. **Results** SAH group and Sham group showed significant reduction of diameter of the basilar artery (28+/-14% and 27+/-9%) on 2 days after the blood injection. However SOD group, diameter of the basilar artery was scarcely changed through follow-up 11 days after the blood injection. **Conclusion** Superoxide anion was suspected to play an important role in the genesis of cerebral vasospasm. This is the first report that h-r SOD can prevent the occurrence of cerebral vasospasm following SAH in vivo study.

SESSION E
Endothelin, Nitric Oxide and Neurogenic Mechanisms in Vasospasm

44 MECHANISMS AFFECTING HEMOGLOBIN-INDUCED SECRETION OF ENDOTHELIN-1 IN CULTURED ENDOTHELIAL CELLS

I. Fuwa, C. Gajdusek, Z. Luo, M.R. Mayberg. *Department of Neurological Surgery, University of Washington, Seattle, WA. USA*

Hemoglobin markedly enhances the secretion of endothelin-1 (ET-1) by endothelial cells in culture. To determine the mechanisms by which hemoglobin mediates ET-1 secretion, cultured bovine aortic endothelial cells were concurrently exposed to hemoglobin and putative agents affecting ET-1 synthesis. Oxyhemoglobin and methemoglobin produced equivalent increases in ET-1 secretion at 4 hours. ^{51}Cr release from endothelial cells was not increased with oxyhemoglobin exposure, suggesting that increased ET-1 in the media was not due to nonspecific cell damage. Inhibitors of mRNA synthesis (Actinomycin D), protein synthesis (cyclohexamide) and proendothelin protease (phosphoramidon) caused equivalent reductions in ET-1 secretion in both control and hemoglobin-treated endothelial cells. Free radical scavengers, including superoxide dismutase, deferoxamine, mannitol and 21-aminosteroid, did not significantly attenuate ET-1 secretion. Similarly, agents modulating protein kinase activity (ATP), endothelium-dependent relaxing factor secretion (acetylcholine, L-arginine) and intracellular cGMP levels (8-bromo-cGMP) did not influence ET-1 secretion in basal or hemoglobin-stimulated endothelial cells. These data suggest that free radicals and EDRF are not involved in the modulation of ET-1 secretion by endothelium.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

45 SUBARACHNOID HEMORRHAGE IMPAIRS ENDOTHELIAL L-ARGININE PATHWAY IN SMALL BRAIN STEM ARTERIES. Z.S. Katušić, and F. Cosentino. Dept. Anesthesiol., Mayo Clinic, Rochester, MN 55905.

The present experiments were designed to determine the effect of subarachnoid hemorrhage (SAH) on endothelium-dependent relaxations to arginine vasopressin (AVP), bradykinin (BR) and calcium ionophore (A23187) in small arteries of the brain stem. In "double hemorrhage" canine model of the disease presence of vasospasm of basilar artery was confirmed by angiography. Secondary branches of control basilar arteries (324±11 μm, n=6) and arteries exposed to SAH for seven days (328±12 μm, n=5) were dissected and mounted on glass microcannulas in organ chambers. Changes in intraluminal diameter of the pressurized arteries were measured using a video dimension analyzer. All experiments were performed in the presence of indomethacin (10^{-5}M). In control arteries, during contractions induced with prostaglandin H_2/thromboxane A_2 receptor agonist U46619 ($3x10^{-8}$M-10^{-7}M), AVP (10^{-11}M-10^{-7}M), BR (10^{-10}M-10^{-6}M) and A23187 (10^{-8}M-10^{-6}M) caused concentration-dependent relaxations. The removal of endothelium abolished these relaxations. A nitric oxide synthase inhibitor N^G-nitro-L-arginine methyl ester (L-NAME; 10^{-4}M and $3x10^{-4}$M) abolished relaxations to AVP and produced small but significant rightward shift of concentration-response curves to BR and A23187. SAH abolished endothelium-dependent relaxations to AVP but did not affect the relaxations to BR or A23187. These studies suggest that in small arteries of the brain stem AVP causes relaxations by activation of endothelial L-arginine pathway. This mechanism of relaxation is impaired by SAH. In contrast, endothelial L-arginine pathway appears to play a limited role in relaxations resistant to SAH.

46 ENDOTHELIUM-DEPENDENT REACTIVITY OF CANINE BASILAR ARTERY DURING CHRONIC CEREBRAL VASOSPASM. F. Cosentino, Z.S. Katušić. Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905.

Impairment of endothelium-dependent relaxations has been reported in a number of vascular diseases including vasospasm of cerebral arteries following subarachnoid hemorrhage (SAH). The present study was designed to determine the effect of SAH on endothelium-dependent contractions. In dogs, SAH and vasospasm were induced by percutaneous injections of autologous venous blood into cisterna magna. Rings of control and vasospastic basilar arteries were suspended in Krebs-Ringer bicarbonate solution gassed with 94% O_2 and 6% CO_2 (t = 37°C; pH = 7.4). Changes in isometric tension were recorded continuously. In control arteries contracted with uridine 5'triphosphate (UTP; 10^{-5}M), calcium ionophore A23187 (10^{-9}-10^{-6}M) caused endothelium-dependent contractions. SAH did not affect these contractions. Indomethacin (10^{-5}M) or prostaglandin H_2/thromboxane A_2 receptor antagonist SQ29548 (10^{-6}M) reversed A23187-induced contractions into endothelium-dependent relaxations. These relaxations were significantly reduced in arteries exposed to SAH. Our studies confirmed earlier observations suggesting that an impairment of endothelium-dependent relaxations may contribute to development of cerebral vasospasm. In contrast, it appears that endothelium-dependent contractions mediated by arachidonic acid metabolism via the cyclooxygenase pathway do not play an important role in chronic narrowing of cerebral arteries following SAH.

47 CELLULAR MECHANISM OF ENDOTHELIN-1 PRODUCTION BY OXYHEMOGLOBIN IN CULTURED ENDOTHELIAL CELLS
H.Kasuya, B.Weir, K.Stefansson. Section of Neurosurgery and Department of Neurology, University of Chicago

Release of endothelin-1 (ET-1) from cultured endothelial cells has been shown to be stimulated by oxyhemoglobin (oxyHb). To elucidate the cellular mechanisms, we tested the effects of several compounds on the oxyHb-induced ET-1 release.

OxyHb produced concentration-dependent (0.1-10 uM) and time-dependent (0-24 hr) increases in immunoreactive (ir) ET-1 in cultured bovine endothelial cell-condition medium. Immunoreactive (ir) ET-1 levels stimulated by oxyHb (5 uM) methemoglobin (5 uM), thrombin (10 U/ml), and 5 % serum were approximately 7, 5.5, 1.5, and 9-fold over basal condition, respectively. Increase in intracellular cAMP by beta-adrenergic agonist, isoproterenol (10 uM) or 8-bromo cAMP (1 mM) and increase in intracellular cGMP by 8-bromo cGMP (1 mM) did not significantly affect oxyHb-induced ir ET-1 production. An inhibitor of nitric oxide synthase, L-NG-monomethyl arginine (200 uM) and soluble guanylate cyclase inhibitor, methylene blue (10 uM) did not significantly potentiate oxyHb-induced ir ET-1 production. Nicardipine (10 uM) did not inhibit this effect. Staurosporine (0.1 uM), a protein kinase C (PKC) inhibitor, significantly inhibited oxyHb-induced ir ET-1 production.

These results suggest that oxyHb stimulates ET-1 release by a mechanism that may involve, in part, the activation of PKC.

48 ROLE OF ENDOTHELIN-1 AND ET_A RECEPTOR IN DELAYED CEREBRAL VASOSPASM FOLLOWING SUBARACHNOID HEMORRHAGE S.Itoh, K.Ide, T.Sasaki, K.Takakura
Department of Neurosurgery, Faculty of Medicine, University of Tokyo, Tokyo, Japan

The pathogenetic mechanism of delayed cerebral vasospasm following subarachnoid hemorrhage(SAH) has not been clarified yet. We examined an action of endothelin-1(ET-1) and ET_A receptor in that pathological condition using canine two-hemorrhage SAH model. 1)In the SAH model, an ET_A receptor antagonist, BQ-485 or BQ-123, was continuously administered, systemically or intrathecally, respectively. The basilar artery narrowing on the angiogram was measured on Day 7. ET_A receptor antagonists prevented the narrowing of canine basilar artery either by systemic administration (75% vs 60% in control, $p<0.01$) or by continuous intrathecal injection (97.6% vs 70.7% in control, $p<0.05$). 2)Using the northern blot analysis, expression for messenger ribonucleic acid(mRNA) coding ET_A receptor was measured on Day 0(pre-SAH), Day 3, Day 7 in the SAH model. The expression for ET_A mRNA was distinctly increased on day 3 after SAH, and was also detected on day 7 after SAH more than on day 0. Recently, the dysfunction of endothelium dependent relaxation caused by endothelial injury is thought to yield the cerebral vasospasm after SAH. But ET-1 could play some important roles in cerebral vasospasm, because ET_A receptor antagonists dose-dependently inhibit the narrowing of basilar artery in the present study. In addition, an increment of the expression of ET_A receptor mRNA on Day 3 after SAH suggests that the vascular smooth muscle cell is sensitized for ET-1 in the earlier phase following SAH.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

49 The role of endothelin-1 in the origin of cerebral vasospasm

Ryuta Suzuki, Hiroyuki Masaoka, Yukio Hirata, Fumiaki Marumo, Eiji Isotani, and Kimiyoshi Hirakawa.
Department of Neurosurgery, Tokyo Medical and Dental University, Tokyo, Japan.

We investigated plasma and cerebrospinal fluid (CSF)concentrations of endothelin-1 like immunoactivity (ET-1-LI) in 27 patients with subarachnoid hemorrhage (SAH) serially. Plasma ET-1-LI in patients with SAH were higher than those in normal subjects. Plasma ET-1-LI in patients with vasospasm were higher than those in patients without vasospasm during the first week of the SAH. CSF ET-1-LI in patients with vasospasm rose significantly in the second week of SAH, although, CSF ET-1-LI in patients without vasospasm were within normal range during whole periods of observations.

We hypothesized that the endothelial cell injury has the key role of the origin of the vasospasm. Endothelial injury causes functional disturbance of endothelial derived relaxing factors (EDRF), therefore the enhancement the effect of the endothelial derived contracting factor (EDCF) occur. The mechanisms of the occurrence of endothelial injury will be discussed.

50 EFFECTS OF ENDOTHELIN ON RABBIT BASILAR ARTERIES

R.Ogawa, T.Ohta, S.Kazuki, M.Tsuji, Y.Tamura, Y.Yoshizaki, T.Takase, K.Yamada.
Department of Neurosurgery, Osaka Medical College, Osaka, JAPAN

Introduction : The differential effects of intra- and extraluminal endothelin (ET) on rabbit basilar arteries were examined, using our perfusion system with which the vasoactive agents can be administered selectively to intra- or extraluminal space. We also examined whether extraluminal oxyhemoglobin (oxyHb) affects the effect of ET.

Methods : Basilar, femoral and mesenteric arteries of Japanese white male rabbits were surgically isolated and prepared as cylindrical sections, which were perfused at a constant flow rate in our perfusion system. Contraction or dilatation of the preparation was recorded as increase or decrease of perfusion pressure gradient by a differential pressure gauge. 1) ET ($3\times10^{-10}\sim3\times10^{-8}$ M) was applied selectively to the intra- and extraluminal space of each arteries in a cumulative manner. 2) After extraluminal pretreatment with 10^{-5} M oxyHb, ET($10^{-10}\sim3\times10^{-8}$ M) was applied selectively to intra- and extraluminal space of basilar arteries in a cumulative manner.

Results : 1) In each preparations, ET caused dose-dependent contractions. Basilar artery was more sensitive to ET than femoral and mesenteric arteries. There were no significant differences between intra- and extraluminal ET. 2) Extraluminal oxyHb significantly potentiated the ET-induced contraction.

Conclusions : Intraluminal ET may be a specific vasoconstrictor of cerebral arteries and its effect may be enhanced by oxyHb in the subarachnoid space. This may play some role in the pathogenesis of cerebral vasospasm.

51 EFFECT OF ENDOTHELIN$_A$ RECEPTOR ANTAGONIST AND PHOSPHORAMIDON ON CEREBRAL VASOSPASM

F. Cosentino, E.G. McMahon*, J.S. Carter**, Z.S. Katušić. Dept. Anesthesiol., Mayo Clinic, Rochester, MN 55905, *G.D. Searle & Co. and **Monsanto Co., St. Louis, MO 63167.

The present study was designed to determine whether an endothelin$_A$ (ET_A) receptor antagonist BQ-123 (cyclo[Dtrp, Dasp, pro-D-val-Leu]) or an endothelin converting enzyme inhibitor phosphoramidon may prevent development of cerebral vasospasm following subarachnoid hemorrhage (SAH). A "double hemorrhage" canine model of the disease was used (n=17 dogs) and the degree of vasospasm of the basilar artery was assessed by angiography. Mongrel dogs of either sex were divided into three experimental groups: animals treated with daily intracisternal injections of BQ-123 (10^{-4}M; n=6), or phosphoramidon (2×10^{-4}M; n=6) and control animals treated with saline solution (n=5). Diameter of basilar arteries in animals treated with saline solution was reduced by SAH to 56±7% of control diameter. BQ-123 and phosphoramidon did not significantly affect SAH-induced vasospasm (diameters were 62±0% and 56±10% of control diameters for BQ-123 and phosphoramidon, respectively). In contrast, in isolated canine basilar arteries BQ-123 (10^{-5}M) selectively inhibited concentration-dependent contractions to ET (10^{-11}-3×10^{-8}M; n=5). Levels of immunoreactive ET in plasma and cerebrospinal fluid were not affected by development of vasospasm. These results suggest that a) intracisternal injections of ET_A receptor antagonist or phosphoramidon can not prevent SAH-induced cerebral vasospasm and b) endothelin may not be the major mediator responsible for the decrease in cerebral arterial diameter associated with SAH.

52 EFFECTS OF ET_A RECEPTOR ANTAGONIST ON NORMAL AND SPASTIC CANINE BASILAR ARTERIES

K.Ide, S.Ito, T.Sasaki, T.Kirino. Department of Neurosurgery, University of Tokyo, Tokyo

In order to investigate the role of endogenous endothelin (ET) and ET_A receptor in normal and spastic canine basilar arteries following experiments were performed with novel potent ET_A receptor antagonist BQ-123Na (BQ).

in vitro study: Effects of BQ on the contractions induced by various spasmogens (ET-1, $PGF_{2\alpha}$ 5-HT, human hemolysate, bloody CSF) in isolated canine basilar arteries were tested using an isometric tension recording method. in vivo study: 0.6mg/kg of BQ was administered intrathecally to normal dogs, one-hemorrhage models in day 2, and two-hemorrhage models in day 4. Changes of the caliber of the basilar artery were measured by angiography

BQ shifted the ET-1 induced concentration-response curve to the right in a parallel fashion with a pA_2 value of 7.35 but did not significantly affect contractions by other agonists. Intrathecally injected BQ induced gradual dilatation of the basilar artery which lasted for more than 24 hours both in normal and SAH model dogs. These results suggest that endogenous endothelin may contribute to the control of basal tonus of cerebral arteries and also to the pathogenesis of vasospasm together with the impairment of cerebroarterial relaxing mechanisms.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

53 REVERSAL OF SAH-INDUCED VASOCONSTRICTION USING AN ENDOTHELIN RECEPTOR ANTAGONIST

H.H. Caner, P.L. Foley, N.F. Kassell, K.S. Lee. Department of Neurosurgery, University of Virginia, Charlottesville, VA 22908

Recent reports indicate that endothelin (ET) synthesis is increased after subarachnoid hemorrhage (SAH). The participation of ET in the etiology of vasospasm, however, remains a matter of discussion. To investigate this issue, an endothelin receptor antagonist (ETant), cyclo(D-Asp-L-Pro-D-Val-L-Leu-D-Trp), was tested for its ability to reverse vasoconstriction following SAH. A transclival surgical approach to the basilar artery in rabbits was utilized, and the arterial diameter measured continuously using videomicroscopy. Artificial CSF was topically appplied to the basilar artery for 40 minutes in all animals prior to application of other agents. Rabbits were divided into four groups: (1) normal rabbits treated with ETant only (40ηM) (2) normal rabbits treated with 50mM KCl, then 50mM KCl + 40ηM ETant; (3) normal rabbits treated with 20ηM ET-1, then 20ηM ET-1 + 40ηM ETA; and (4) Rabbits subjected to SAH and treated with 40ηM ETA.

In normal (non-SAH) rabbits, ETant: a) had little or no effect on resting tone, b) did not reverse KCl-induced constrictions, and c) substantially reversed ET-induced constrictions. In rabbits with SAH, the 'resting' diameter of the basilar artery was 64% of the resting diameter in normal animals. ETant reversed this SAH-induced constriction by 71%. These findings support the hypothesis that an increased activation of ET receptors in the basilar artery contribute to cerebral vasospasm following SAH.

54 ALTERATIONS IN REACTIVITY OF HUMAN CEREBRAL ARTERIES AFTER SUBARACHNOID HEMORRHAGE

H. Onoue, N. Kaito, S. Tokudome*, T. Abe, M. Nakajima, Y. Akazaki, and N. Nakamura.
Division of Neurosurgery, The Jikei University School of Medicine, Tokyo, and *Tokyo Medical Examiner's Office, Tokyo, Japan.

The present study was undertaken to clarify the modification by subarachnoid hemorrhage (SAH) of responsiveness of human cerebral arteries to vasoactive substances. Isometric tension was measured in helical strips of basilar and middle cerebral arteries isolated from human cadavers. Contractions caused by K^+, $PGF_{2\alpha}$, norepinephrine, and serotonin were reduced in arteries obtained from patients of aneurysmal SAH compared with those from patients of extracranial diseases. Endothelium-dependent relaxations elicited by substance P and bradykinin, and -independent relaxations caused by PGI_2 and nitroglycerin were also markedly inhibited after SAH. However, the reduction of relaxations induced by PGI_2 was significantly less than that of relaxations by substance P, bradykinin, and nitroglycerin. The impairment of these contractile and relaxant responses after SAH revealed a marked regional difference. A degree of the impairment tended to correlate with a volume of subarachnoid blood clots surrounding the arteries or with a distance from the site of a ruptured aneurysm.
These results indicate that the contractile and relaxant functions of human cerebral arteries are severely damaged after SAH, and suggest that the decreased relaxant responses to vasodilators may result predominantly from a dysfunction of smooth muscle cells.

55 MECHANISMS OF ACTION OF BRADYKININ, SUBSTANCE P AND VASOPRESSIN IN HUMAN CEREBRAL ARTERIES

N. Kaito, H. Onoue, S. Tokudome*, S. Nakahara, T. Fuse, N. Nakamura.
Department of Neurosurgery, The Jikei University School of Medicine, Tokyo, and *Tokyo Medical Examiner's Office, Tokyo, Japan.

We examined mechanisms of action of bradykinin (BK), substance P (SP), and vasopressin (VP) in human cerebral arteries to obtain a better understanding of humoral control of cerebrovascular tone. Middle cerebral and basilar arteries were isolated from human cadavers during autopsy within 12 hours postmortem, and isometric tension was measured in helical strips of the arteries. Both BK and SP relaxed these regionally different arteries precontracted with $PGF_{2\alpha}$ to a similar extent. The relaxations elicited by BK and SP were abolished almost completely by removal of the endothelium, and were reduced significantly by pretreatment with nitro-arginine, an inhibitor of EDRF-synthesis. Treatment with indomethacin, a cyclooxygenase inhibitor, did not affect the relaxations. On the other hand, VP predominantly produced a concentration-dependent contraction in human cerebral arteries. However, a few specimens of basilar arteries, but none of middle cerebral arteries, responded to VP with an endothelium-dependent relaxation. The contraction caused by VP of middle cerebral arteries was greater than that of basilar arteries. These results indicate that responses of human cerebral artery to BK and SP are mediated by EDRF and that the function of VP receptors differs in basilar artery versus middle cerebral artery.

56 CYCLOPIAZONIC ACID RELEASES NITRIC OXIDE FROM ENDOTHELIUM BY INCREASING CALCIUM INFLUX THROUGH NONSELECTIVE CATION CHANNELS

H. Zhang, E.E. Daniel and B. Weir. Department of Biomedical Sciences, McMaster University, Hamilton, Ontario and Department of Neurosurgery, The University of Chicago, Chicago, Illinois.

Cyclopiazonic acid (CPA), an inhibitor of the sarcoplasmic reticulum calcium pump, relaxes vascular smooth muscle by increase of intracellular calcium in endothelial cells and release of EDRF. No evidence suggested the presence of the L-type calcium channels in endothelial cells, but the nonspecific cation channels which are permeable to calcium have been suggested to mediate calcium influx into endothelial cells. We used patch-clamp techniques to study the effects of CPA in cultured bovine pulmonary arterial endothelial cells and human umbilical vein endothelial cells. In whole-cell patch-clamp, CPA (3-20 uM) increased an outward K current which is sensitive to TEA (1-3mM) and 4-AP (1 mM), but not to gibenclamide (1-10 uM). Depletion of extracellular calcium or increase pipette EGTA concentration (11 mM) attenuated the effects of CPA, which suggested that CPA increases intracellular calcium and activates calcium-dependent K channel. In cell-attached study, CPA activated an outward K current. When pipette contains either 120 mM CaC12 or 140 mM NaCl (plus 5 mM CaC12), CPA (10 uM) increased an inward conductance of 30 pS. The effects of CPA was reversible by washing. We conclude that CPA induces calcium influx through the nonspecific cation channels and activates calcium-dependent K channels by blocking calcium uptake into and leaking from calcium stores of endothelial cells. These effects of CPA may supply calcium to activate nitric oxide release and modulate vascular smooth muscle contraction.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

57 **ROLE OF MEMBRANE POTENTIAL IN VASOSPASM AFTER SUBARACHNOID HEMORRHAGE (SAH).**
M.Zuccarello, C.L.Bonasso, R.M.Rapoport, N.Sperelakis VAMC and Departments of Neurosurgery, Pharmacology, and Physiology University of Cincinnati College of Medicine Cincinnati, Ohio 45267-0515

This study investigated the effect of SAH on vascular smooth muscle cell (VSMC) membrane potential. SAH was induced in rabbits by percutaneous injection of 1 ml/Kg autologous nonheparinized arterial blood into the cisterna magna. Animals were sacrificed 2 days after SAH and the basilar artery dissected and used for electrophysiological studies. VSMC impalements were made from the adventitial side. SAH depolarized the membrane to -37±1 mV (N=15) from a control value of -49±1 mV (N=28) (P<.05). Cromakalim (0.1 -10μM) dose-dependently reversed the SAH-induced membrane depolarization to control levels. Cromakalim-induced membrane repolarization was prevented by the K_{ATP} channel blocker, glyburide (10 μM). We also tested whether decreased release of endothelium-dependent relaxing factor (EDRF) could account for the SAH-induced membrane depolarization. The inhibitor of EDRF release, L-NNA (0.3mM), produced a similar amount of depolarization as SAH, namely to -41±1 mV (N=5) (P=NS). Removal of the endothelium also depolarized the membrane to a similar value as SAH, -40±1 mV (N=5) (P=NS). The results suggest that 1) SAH-induced membrane depolarization may be due to inactivation of K_{ATP} channels; 2) the depolarization can be completely accounted for by decreased EDRF release, and 3) membrane depolarization may account, at least in part, for SAH-induced vasospasm.

58 EFFECTS OF THE TIMING OF CLOT REMOVAL ON PHARMACOLOGICAL RESPONSES IN A MODEL OF CEREBRAL VASOSPASM IN THE MONKEY
T. Tsuji[1], D.A. Cook[2], B.K.A. Weir[3], Y. Handa[4] Departments of Neurosurgery at [1]Shinshu University, Matsumoto, [4]Fukui Medical School, Fukui, [3]University of Chicago, Chicago and [2]Department of Pharmacology, University of Alberta, Edmonton.

It is believed that to minimise cerebral vasospasm, clotted blood should be removed as early as possible after subarachnoid haemorrhage (SAH). The time during which clot removal remains effective, however, is not clear. In order to examine this question, cynomolgus monkeys were randomized into five groups. In animals in four of the groups, a clot of autologous blood was placed bilaterally around the major vessels in the basal subarachnoid space to mimic SAH, while in the fifth group, saline was instilled into the same region. In three of the groups, the clot was surgically removed after 48, 72 or 96 hours, while in the remaining group the clot was left in place. Animals were sacrificed at seven days, and the middle cerebral arteries were removed, cut into rings, and isometric dose response curves to potassium chloride (KCl), noradrenaline (NA) or 5-hydroxytryptamine (5-HT) were obtained. There was a progressive attenuation of the responses to all agonists in the clot groups when compared with the saline control group, which reached significance at 72 hours in the case of KCl and NA and at 48 hours in the case of 5-HT. This suggests that changes in blood vessel response occur as early as 48 hours after haemorrhage, and thus surgery and clot removal should be considered within the first two days after SAH.

59 TRIGEMINAL AFFERENTS AND BRAINSTEM CENTERS INVOLVED IN THE DEVELOPMENT OF CEREBRAL VASOSPASM IN THE SQUIRREL MONKEY.
N-Aa. Svendgaard, Y. Shiokawa and T. Delgado-Zygmunt. Neurosurgical Department, Karolinska Hospital, S-104 01 Stockholm Sweden.

An experimental subarachnoid hemorrhage (SAH) in the squirrel monkey induced a biphasic vasospasm angiographically with a maximal acute spasm at ten minutes and a maximal late spasm at day six post SAH. CBF - and CMRglu studies produced a global CBF decrease of 25% and an increase in deoxyglucose uptake of about 50 % at day six post SAH.

Lesioning of the A_2 nucleus or the median eminence prior to a SAH, prevented the development of both spasm phases. Intrathecal administration of the substance P antagonist, spantide or SP anti-gammaglobulin hindered spasm development and the blood flow changes seen in control SAH animals.

A unilateral postganglionic trigeminal lesion produced an ipsilateral constriction of the cerebral arteries of 27%. Following a SAH there was an increase of 12% in the degree of spasm on the postganglionically lesioned as compared to the non lesioned side. A unilateral preganglionic lesion did not cause any change in the baseline arterial diameter and following a SAH, the degree of spasm in these animals was similar to that of controls.

Following both unilateral pre- or postganglionic trigeminal lesions per se, there was an increase in deoxyglucose uptake of about 50%. In the preganglionically lesioned animals, there was no further increase in deoxyglucose uptake after a SAH, while the animals with a postganglionic lesion showed a further increase in glucose uptake of close to 50% following cisternal blood injection.

The data indicate that a reflex arc is involved in the development of vasospasm in the squirrel monkey. The findings also show that the trigeminal nerve has a dual function, one peripheral, involving an axonal reflex, the other one comprising central connections. The peripheral or axon reflex mechanism exerts a tonic effect on the cerebral vessel. Following a SAH, the axon reflex seems to attenuate cerebral vasospasm. There is evidence for involvement of the trigeminal system in the regulation of cerebral metabolism.

60 **HUMAN PIAL ARTERY DIAMETER IS REGULATED PRIMARILY BY INTRAVASCULAR PRESSURE AND FLOW.**
R.D. Bevan, J.A. Bevan, A. Klaasen, T. Poseno, T. Wellman, C. Walters*. Totman Laboratory, University of Vermont, College of Medicine, Burlington. *Neurological Surgeons, P.C., Phoenix, AZ

It has been observed that angiographic narrowing of small arteries occurs distal to and often distant from the site of subarachnoid hemorrhage and associated area of chronic vasospasm. An understanding of the basis of changes in pial artery diameter and blood flow accompanying a variety of cerebrovascular disorders depends on an appreciation of the mechanisms that regulate pial artery tone. Recent in vitro studies of human pial artery segments obtained during surgery indicate that activation of perivascular nerves has little effect on smooth muscle tone. Extrapolated to in vivo this suggests that other mechanisms are dominant. Perfused human pial artery segments can develop myogenic tone maintained over a wide intravascular pressure range. Intraluminal flow causes both constriction and dilation depending upon the conditions. Dilator responses are usually dominant. These observations suggest that pial artery tone is regulated by intraluminal pressure and flow. Distal vascular narrowing seen with proximal large vessel constriction could result from a lower distal pressure and smaller passive vascular distention and/or a loss of flow (shear-stress)-induced dilation. The consequences of upstream reductions in diameter are distributed to the distal vascular bed through changes in pressure and flow.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

SESSION F
Structural Cerebral Artery Wall Changes and Vasospasm

61 FUNCTIONAL NARROWING IN CHRONIC CEREBROVASOSPASM IS THE RESULT OF INCREASED WALL STIFFNESS FOLLOWING FUNCTIONAL DAMAGE. J.A. Bevan, R.D. Bevan. Department of Pharmacology, University of Vermont, College of Medicine, Burlington, VT 05405-0068.

Several hypotheses have been proposed to explain the basis of chronic cerebrovasospasm. Our experiments support the conclusion that the arterial narrowing is primarily due to increased wall stiffness and volume resulting from damage. Local vasoactive factors, agonist hypersensitivity, abnormal myogenic tone and contractile behavior may contribute. In the monkey experiments, quantitative modeling of the consequences of decreased wall elasticity indicate that this accounts for a reduction in internal diameter of 40%. The anticipated reduction in the most affected artery would be almost 80%. In the rabbit studies, the papaverine-insensitive component of angiographic narrowing correlates directly with loss of contractility and increase in wall stiffness. That poor contractility reflects artery wall damage is supported by its inverse relationship to stiffness. Observations by ourselves and others of extensive structural change coincident with an inflammatory response and by others of the protective effect of pretreatment with calcium channel blockers and steroids are consistent with this proposal. Our conclusion is that the decreased blood flow seen in chronic cerebrovasospasm results from the resistance of blood vessels in and around the site of hemorrhage to passive dilation.

Supported by USPHS HL 32383.

62 CONTRACTION OF COLLAGEN LATTICES BY SMOOTH MUSCLE CELLS CULTURED FROM VASOSPASTIC ARTERIES W.E. Butler, J. Rajaratnam, H.P. Ehrlich. Wound Healing Laboratory, Shriner Burns Institute and Harvard Medical School, Boston, Massachusetts.

Part of the arterial narrowing of vasospasm might be due to phenomena other than smooth muscle cell (SMC) contraction. Contraction of a cell-populated collagen lattice (PCL) has been shown to be primarily due to cell-collagen interaction and cell motility, rather than cell contraction. To examine the roles played by these phenomena in vasospasm, simultaneous measurements of SMC-PCL contraction and Ca2+ (using the fluorescent Ca2+ indicator Fura2-AM) were made. SMCs isolated from the basilar artery of double subarachnoid hemorrhage (SAH) and control dogs were isolated and grown in culture. Vasospasm SMC-PCLs contracted more than control SMC-PCLs at 48 hours (change in area 28% vs 9%, $p<.05$). The SMC-PCLs were examined with phase contrast and digital fluorescence microscopy. SMCs in the center of the PCLs tended to have a round shape, whereas SMCs from the periphery tended to have a spindle shape. Vasospasm SMC-PCLs (42% vs 20%, $p<.05$). Moreover, the cytosolic Ca2+ concentration ([Ca2+]i) of spindle shaped cells was greater than that of round cells (388 nM vs 104 nM, $p<.05$). However, the [Ca2+]i of spindle and round cells cultured from vasospastic arteries was not significantly different from that respectively of spindle and round cells cultured from control arteries. The increased contraction by vasospasm SMC-PCLs thus correlated with an increased proportion of SMCs having both spindle shape and increased [Ca2+]i. These findings suggest that part of the arterial narrowing of vasospasm might be due to changes in SMC-collagen interaction and SMC cell motility, and implicate a role for Ca2+ in the regulation of these phenomena.

63 Collagen Gene Expression By Human Myofibroblast In Culture T. Shiota, N. Yabuno, S. Asari, T. Ohmoto, Y. Ninomiya*, Y. Yamamoto**, Departments of Neurological Surgery, and *Molecular biology and Biochemistry, Okayama University Medical School, Okayama, Japan, **Department of Neurosurgery, Mayo Clinic, Rochester, MN

Pathophysiology of vasospasm after subarachnoid hemorrhage has been investigated mostly using animal models and human autopsy cases. Recently, we have established cell lines of myofibroblasts from human cerebral arteries in vasospasm and revealed the capacity of these cells to compact the collagen lattice in vitro (Yamamoto et al, Neurosurgery 30 : 337, 1992) .

In this experiment, molecular biological techniques were employed to further characterize human myofibroblasts. We studied the effect of arterial blood, blood fractions, and other agents on collagen gene expression by cultuered myofibroblasts. After exposure to each agent, the cells underwent RNA extraction. The expressions of mRNA of collagens type I, III, IV, and V were measured by Northern blots and dot blots analyses. Type I collagen mRNA level was not influenced by exposure to whole arterial blood or erythrocyte fraction. Factors affecting collagen gene expression by myofibroblasts will be discussed in comparison with those by dermal fibroblasts.

64 EFFECT OF PLATELET-DERIVED GROWTH FACTOR (PDGF) ISOMERS ON CANINE CEREBRAL ARTERY CONTRACTILITY IN EXPERIMENTAL SUBARACHNOID HEMORRHAGE Jiang Kun. Department of Neurosurgery, The First Affiliated Hospital, Dalian Medical College, China.

Platelet-derived growth factor (PDGF) is a potent mitoben for fibro-blasts and vascular smooth muscle cells, and considered to the patho-genesis of wound healing, atherosclerosis, and proliferative change in the major cerebral arteries following subarachnoid hemorrhage (SAH). Recently it has been shown that PDGF is a potent vasoconstrictor. We examined the effects of PDGF in vitro on contractility of the cerebral artery of normal and SAH models.

Using isometric tension-recording system, effects of PDGF isodimers, AA and BB, on isolated canine basilar arteries resected from normal and SAH (double-hemorraged)models were investigated. Both PDGF dimers contracted normal helical strip dose-dependently. Maximal response was produced by 10-11 M order of PDGF dimers, which was in a similar concentration in CSF of human in the acute stage of SAH. In addition, endothelium removal and SAH enhanced the dose-response curves to PDGF dimers.

These results suggest that besides mitogenic activity, PDGF has the spasmogenic activity on the cerebral artery and may play an important role in vasospasm following SAH.

65 PROLIFERATIVE ANGIOPATHY FOLLOWING SUBARACHNOID HEMORRHAGE AND PLATELET-DERIVED GROWTH FACTOR
Y.Honma, T.Kita, S.Inomata, K.Hasui, K.Irie, S.Nagao, *B.R.Clower, *R.R.Smith, Department of Neurological Surgery, Kagawa Medical School, Kagawa, Japan, *Department of Neurosurgery, University of Mississippi Medical Center, Jackson, Mississippi, U.S.A.

Proliferative angiopathy(PA) following subarachnoid hemorrhage(SAH) has been reported to result in arterial narrowing not only due to wall thickening but due to contraction of non-muscle components in the late stage. Platelet-derived growth factor(PDGF) is supposed to be an initiator of PA. The serial studies on the pathogenesis of PA carried out at our institutes are summarized. 1)PDGF content of the cerebrospinal fluid was measured in 13 cases with SAH. Increased PDGF levels(160-3700 pg/ml) were obtained in 10 cases within 4 days after SAH. 2)Intimal accumulation of ^{111}In-labelled platelets in the middle cerebral artery(MCA) was examined in the cat SAH model. Platelet accumulation occured just after SAH and continued more than 3 weeks. 3)Effect of intracisternal injection of rt-PA on the development of PA was examined in experimental SAH. Early removal of cisternal clots significantly inhibited PA. 4)Effect of intracisternal administration of PDGF was examined histopathologically. PDGF B-dimer developed the proliferative changes in the MCA, which were similar to those of the SAH model. These results suggest that PDGF may exert its effects not only from the intima but from the abluminal surface of the vessel, and PDGF(especially B-chain) would be a potent initiator of PA. Removal of cisternal clots and administration of PDGF antagonist in the acute stage of SAH might be clinically useful for prevention of PA.

66 PREVENTIVE EFFECT OF TRAPIDIL ON THE DEVELOPMENT OF PROLIFERATIVE ANGIOPATHY IN EXPERIMENTAL SUBARACHNOID HEMORRHAGE
T.Kita, Y.Honma, S.Inomata K.Hasui, K.Irie, S.Nagao, Department of Neurological Surgery, Kagawa Medical School, Kagawa, Japan

Proliferative angiopathy(PA) following subarachnoid hemorrhage(SAH) is supposed to aggravate cerebral ischemia in relation to late vasospasm. Platelet-derived growth factor(PDGF) has been reported to be a potent initiator of the morphological changes. Preventive effect of trapidil, a specific antagonist of PDGF, on the development of PA was examined in experimental SAH. Twenty-eight cats were randomly divided into 4 groups; a non-surgical control, SAH, trapidil-treated, and trapidil-control groups. SAH was produced by transorbital rupture of the middle cerebral artery(MCA) in both the SAH and trapidil-treated groups. Trapidil(20 mg/kg,i.m.) was administered daily, from 2 days before through 14 days after SAH. The proximal MCA was resected 14 days after SAH and prepared for microscopic examination. For the quantitative analysis, the luminal caliber and wall thickness were calculated(the mean values of the non-surgical group were defined as 100%). The mean values of the luminal caliber and wall thickness were 70%, 100% and 136%, 106% respectively in the SAH and trapidil-treated groups. In the SAH group, degeneration and denudation of the endothelium, subendothelial proliferation of myofibroblast, and increased extracellular matrix were common findings. These were less frequent in the trapidil-treated group. The results showed that the proliferative changes occured in the MCA in experimental SAH were significantly suppressed by trapidil. Trapidil may be clinically useful for prevention of PA, which would be initiated by PDGF.

67 THE PREVENTIVE EFFECT OF STEROIDS IN NON-MUSCLE ARTERIAL CONSTRICTION FOLLOWING SUBARACHNOID HEMORRHAGE
K. Iwasa, R.R. Smith, D.H. Bernanke*, Y. Terai. Departments of Neurosurgery and Anatomy*, University of Mississippi Medical Center, Jackson, MS

The effectiveness of high dose corticosteroids to prevent vasospasm has been reported both clinically and experimentally. We evaluated inhibitory effects of several kinds of steroids, methylprednisolone (MP), hydrocortisone (HC), and 21-aminosteroid (U74006F)(AS) in non-muscle arterial constriction using our in vitro model, the myofibroblast populated collagen lattice (MfPCL). Cell lines of human cerebral artery myofibroblasts were established in our laboratory by explantation culture of arteries obtained from vasospasm victims. We reported that these cells generated force "compacting" the collagen gel matrix by a mechanism distinguishable from smooth muscle contraction, and CSF obtained from vasospasm patients accelerated this compaction. MP caused 56.0% ($p<0.05$) and 33.3% ($p<0.05$) inhibition, HC caused 39.0% ($p<0.01$) and 29.8% ($p<0.05$) inhibition at 10^{-5}M and 10^{-6}M, respectively. Furthermore, these two steroids inhibited enhancing effect of CSF completely. However, AS did not show any inhibitory effect in MfPCL compaction. Our culture model showed the inhibitory effects of corticosteroids in MfPCL compaction, and suggested clinical benefit of using high dose corticosteroids to prevent non-muscle arterial constriction after SAH.

68 CALCIUM MOBILIZATION AND ORGANIC ALTERATIONS IN THE ARTERIAL WALL AFTER SUBARACHNOID HEMORRHAGE
S. Nakamura, K. Yoshida, M. Nakano, H. Watanabe, T. Tsubokawa. Department of Neurological Surgery, Nihon University School of Medicine, Tokyo, 173

Patients suffering from aneurysmal subarachnoid hemorrhage (SAH) were included in the present study. All patients died of vasospasm (CV) as confirmed by angiography and the clinical symptoms. The main arteries showing vasospasm on angiogram were dissected out, and the modified KPS staining technique described by Bogers et al. was employed for the detection of calcium ion with an electron microscope.

Deformation of endothelial cells and distorted smooth muscle cells were observed in the cases of CV. Several vacuoles were found adjacent to the nucleus. Reaction products of calcium ions were present surrounding or within these vacuoles, but were not prominently distributed in the area of smooth muscle cells showing no evidence of morphological changes.

In agreement with our previous studies, the maximum increase of calcium ions in the smooth muscle cells of vessels subjected to SAH was confirmed to be restricted to the early stage of SAH. These results indicated that the increased level of calcium ions in smooth muscle cells caused by SAH do not play a direct role in the persistent contraction of the vessels. Furthermore, the reaction products of calcium ions in the vessels detected at the CV stage may be related to morphological changes of the vessels that are involved in the etiology of CV as a result of calcium overloading at the early stage of SAH.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

69 EXPRESSION OF INTERCELLULAR ADHESION MOLECULE 1 ON CEREBRAL ARTERIES AFTER SUBARACHNOID HEMORRHAGE IN RATS. Y. Handa, M. Kaneko, Te. Kubota, A. Tsuchida, H. Kobayashi, T. Kubota. Department of Neurosurgery, Fukui Medical School, Fukui, Japan

In order to study how immune/inflammatory responses are involved in the pathogenesis of the cerebral vasospasm after subarachnoid hemorrhage (SAH), the kinetics of expression of the intercellular adhesion molecule 1 (ICAM-1), a ligand for the leukocyte adhesion receptor, were studied on the cerebral arteries and parenchymal microvessels following SAH in rats.

The experimental SAH was induced by intracisternal injection of autologous arterial blood in the Sprague-Dawley rats. The rats were sacrificed 1 to 7 days following SAH. The whole brain was immediately frozened by nitrogen liquid. Serial cryostat sections of the brain were prepared and incubated with anti rat ICAM-1 antibody.

Morphometric analysis of the basilar artery showed significant narrowing of the internal caliber of vessels on Day 2 to Day 5 following SAH. In the non-treated control animals, none or weak expression of ICAM-1 was observed on the endothelium of the basilar artery. There was greater expression of ICAM-1 on the endothelium of the basilar artery in SAH rats with a survival time of 1 to 7 days. The expression of ICAM-1 was observed also in the medial layer of the smooth muscle cells of the artery on Day 2 to Day 5 following SAH. The brain parenchyma in the SAH rats showed numerous number of vessels stained with ICAM-1 antibody through the period of Day 1 to Day 7 following SAH, while in the normal rats, the expression in the microvessels were weak and only some vessels could be positively stained.

The present results suggest following issues; both endothelial and smooth muscle cells become targets of immune damage which may be elicited by SAH, and the induction of ICAM-1 on tissues may be an important step in the development of the inflammatory response in the arterial wall resulting in the development of cerebral vasospasm. Great expression of the ICAM-1 in the parenchymal microvessels is thought to influence on the development of brain edema following SAH .

70 ANTI-PHOSPHOLIPID ANTIBODIES IN CEREBRAL VASOSPASM FOLLOWING SUBARCHNOID HEMORRHAGE Y. Hirashima, S. Endo, M. Kurimoto, E. Tsukamoto, A. Takaku. Department of Neurosurgery, Toyama Medical & Pharmaceutical University and Department of Neurosurgery, Tsukamoto Neurosurgical Hospital, Toyama-shi, Toyama, Japan

We studied the role of anti-phospholipid antibodies in vaso- spasm following subarachnoid hemorrhage (SAH). Eleven of 32 patients (34.4%) with SAH had anti-phospholipid antibodies. The incidence of lupus anticoagulants (25%) and anti-cardiolipin IgG (12.5 %) were high. However, anti-phospholipid antibodies disappeared in 4 of 6 patients (67%) reexamined 7 to 13 days following SAH. Symptomatic vasospasm in the antibody-negative group tended to be transient and reversible, while that in the antibody-positive group was more continuous and irreversible, and outcome was worse in patients with anti-phospholipid antibodies than that without ($p < 0.05$). The minimum platelet count was the smallest in patients with symptomatic vasospasm in anti-phospholipid antibody positive group among both antibody-positive and negative groups ($p < 0.05$). Platelet aggregation was increased in anti-phospholipid antibody-positive patients than in antibody-negative patients. The concentration of plasma PF4 was the highest in patients with symptomatic vasospasm in antibody-positive group among the antibody-positive and negative groups ($p < 0.05$). The results suggest that anti-phospholipid antibodies affect the SAH prognosis of the patient during the advanced stage of vasospasm after SAH, perhaps by activating platelets or promoting platelet aggregation.

71 CISTERNAL TALC INJECTION CAN INDUCE A DELAYED AND PROLONGED BASILAR ARTERIAL CONSTRICTION RESEMBLING VASOSPASM AFTER SUBARACHNOID HEMORRHAGE IN DOG K. Nagata*1, H. Nikaido, E. Kobayashi, T. Mori*2, H. Ooami, P. Kim*3, T. Sasaki, T. Kirino. *1Dept of Neurosurgery, New Tokyo Hospital, Matsudo, Chiba, *2Division of Pathology, Institute of Gerontology, Nippon Medical School, Kawasaki, Kanagawa, *3Department of Neurosurgery, University of Tokyo, Bunkyo-ku, Tokyo, Japan

To clarify the possible role of inflammation in the pathogenesis of cerebral vasospasm, we examined the effect of cisternal talc injection in dogs. Talc is known to cause non-immunological inflammation with granuloma formation. Steriled talc powder was suspended in saline, and was percutaneously injected into cisterna magna. The basilar artery constricted up to 61.5±2.2% of the original diameter on day 2. This constriction was continued to day 7 (62.6±3.5%). The diameter 1 hour after injection was 98.5±3.0%, indicating that so-called early spasm was not induced by talc injection. Histological examination revealed corrugation of elastic lamina, detachment of endothelial cells, vacuolar formation in smooth muscle, all of which were anologous to those reported in the spasm artery after subarachnoid hemorrhage. Pharmacological studies *in vitro* showed that the maximal contraction to KCl was moderately diminihed even on day 2 and severely decreased on day 7. It also showed that endothelium-dependent relaxation was abolished while endothelium-independent relaxation was preserved. These pharmacological properties were also quite similar to those observed in the artery with vasospasm. These results strongly suggests the possible role of non-immunological inflammation in the pathogenesis of vasospasm.

72 ULTRASTRUCTURAL CHANGES OF THE CANINE BASILAR ARTERY IN THE CISTERNAL TALC INJECTION MODEL H.Nikaido. (#1) K.Nagata.(#1) T.Mori. (#2) H.Ooami.(#2) T.Sasaki.(#3) T.Kirino. (#3) #1 Department of Neurosurgery, New Tokyo Hospital, Matudo, Chiba,Japan. #2 Division of Pathology, Institute of Gerontology,Nippon Medical School. #3 Department of Neurosurgery,University of Tokyo.

We have previously reported that cisternal talc injection could induce the delayed and prolonged constriction of the canine basilar artery.The main purpose of this ultrastructural study is to investigate the mechanism of this constriction comparing to autologous blood injection model.The canine basilar arteries were examined with electron microscopy on day 2 and day 7 after sterile talc powder injected.A marked constriction was already noticed even on day 2 and lasted to day 7.On day 2,the elastic lamina were folded,corrugated and partly torn off.Smooth muscular cells of the tunica media migrated into the intima.Subintimal proliferation were observed. Endothelial cells were desquamated,contained intracytoplasmic vacuoles and partly detached from the elastic lamina.On day 7, these ultrastructural changes were more prominent,but were basically identical with those on day2. These histological changes were very similar to those reported in subarachnoid hemorrhage model,although the changes were more prominent in talc model.Thus,simple talc injection induced an analogous histological changes in canine basilar artery. These results suggest that non-immunological inflammation may play a more important role for the pathogenesis of vasospasm.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

73 **CHARACTERIZATION OF AN ANTERIOR CIRCULATION RAT SAH MODEL**

C. Thomé, A. Piepgras, and P. Schmiedek. Dept. of Neurosurgery, Ludwig-Maximilians-Universität München, 8000 München 70, Germany

The rat model is frequently used to investigate changes following SAH attributed to vasospasm (VSP). The occurence of VSP in the rat model is based on an angiographically controlled study of the posterior circulation (1). For microcirculatory studies, however, a model involving the middle cerebral artery (MCA) is more appropriate. We discuss the possibilities and limitations of an anterior circulation rat SAH model.

Material & Methods:
Male Wistar rats (300-350 g body weight) were used in this study. Control angiography of the left ICA, MCA, and stapedial artery (an extracranial branch of the ICA in the rat) was performed via catheterization of the left external carotid artery (ECA). SAH was induced by percutaneous puncture of the chiasmatic cistern followed by injection of 0.3 ml fresh autologous arterial blood. Before, during, and following SAH (30') ICP and changes in cerebral blood flow (Laser Doppler flowmetry) were continuously measured. 2 days following SAH a second angiographic study was carried out followed by perfusion fixation and histological examination. The angiographies were evaluated using video-morphometry.

Results:
Mortality in this model is 15%. Multiple angiographic studies are possible: 2 days following SAH a vasoconstriction (20%) of the MCA was noted. Further data concerning ICP-, and CBF-changes, as well as follow-up angiographic studies (2-7 days) will be presented.

Conclusion:
A SAH primarily involving the anterior fossa is possible in the rat. An angiographically visible vasoconstriction in the MCA is present, justifying further studies.

Reference:
1. T. J. Delgado, J. Brismar, N. A. Svendgaard, *Stroke* 16, 595-602 (1985).

74 Ultrastructure of Myoendothelial Junctions in Middle Cerebral Arteries of Cats After Subarachnoid Hemorrhage Y. Yamamoto*, T. Ohmoto, K. Ogiwara, T. Shiota, N. Yabuno, S. Asari *Department of Neurosurgery, Mayo Clinic, Rochester, MN, Department of Neurological Surgery, Okayama University Medical School, Okayama, Japan

Myoendothelial junctions (MEJs) in the middle cerebral arteries were studied morphologically using the transmission electron microscope after experimental subarachnoid hemorrhage (SAH) . Seven cats underwent injection of 2.5 ml arterial blood into the suprasellar and sylvian cisterns (SAH group) . They were sacrificed by perfusion-fixation 4 hours after blood injection. Control animals were also sacrificed by perfusion -fixation without surgical intervention. Transmission electron microscopy revealed that MEJs were of two types, "gap-like" and "synaptic." The latter contained a variety of intracellular vesicles. Arteries exposed to subarachnoid blood demonstrated degenerative changes of MEJs, numerous vacuoles, and loss of microfilaments. Quantitative study using serial sections failed to show a significant difference in the number of both types of junctions between the control and SAH groups. The ultrastructural alteration of MEJs may provide further morphological evidence for endothelial regulation of vascular contractility by chemical mediator.

75 ACTIONS OF CALCIUM ANTAGONISTS IN SAH.
N. Dorsch. Dept of Neurosurgery, Westmead Hospital, Sydney, Australia.
These drugs, used in delayed ischemia after SAH, have several possible mechanisms:
1. Prevention or reversal of spasm. Calcium influx into vascular muscle cells is decreased. In some cases only, intracarotid injection of nimodipine reverses angiographic spasm.
2. Opening of collateral vessels. Nimodipine is particularly effective on arterioles. Where CBF improves without change in angiospasm or TCD velocity, this may be the mechanism.
3. Protection at neuronal membrane level. In ischemia, neuronal intracellular calcium rises much less with nimodipine. Many patients improve clinically even when blood flow falls.
4. Intracellular protection. An intracellular mechanism via inhibition of L-type membrane channels, or effects on calmodulin and/or protein kinase C, is possible. Nimodipine prevents ornithine decarboxylase entry in ischemia.
5. Blood and rheology. Improved erythrocyte deformability has been postulated. Reduced calcium-dependent platelet aggregation with nifedipine has been shown. There is also decreased release by platelets of thromboxane B2.
6. Influence on mitogenesis. Studies suggest that the mitogenic effect of agonists such as endothelin may be lessened, preventing vascular muscle cell proliferation in vasospasm.
7. Effect on fluid management. Hypotension may occur with calcium antagonists, necessitating increased fluids. This can by itself help.

76 REVIEW OF MANAGEMENT OF CEREBRAL VASOSPASM.
N. DORSCH. Department of Neurosurgery, Westmead Hospital, Sydney, Australia.
A literature review of cerebral vasospasm showed delayed ischemic deficits (DID) occurred in 32.5% of cases. The outcome of 5385 patients with DID was: death 31.9%, permanent deficit 33.0%, good outcome 35.1%.
Induced hypervolemia +/- hypertension +/- hemodilution as prophylaxis was reported in 2098 cases, with DID occurring in 351 (16.7%). For treatment of DID in 2372 patients, the death rate was 17.1%, disabilities 28.9%, and good outcomes 54.3%, an improvement over the natural history especially in death rate.
In controlled studies of nimodipine prophylaxis, DID was 31.7% in 978 controls and 22.4% in 702 with nimodipine prophylaxis (χ^2 = 17.3, $P < 0.0001$). Outcome was also better, with 28.4% bad outcomes in 1166 controls and 19.6% in 923 treated (χ^2 = 21.0, $P < 0.0001$). For all published reports with nimodipine, DID occurred in 13.2% of 3403 cases. With nimodipine treatment of DID, death rate (in 638 patients) was 17.3%, disability 24.9%, and good outcomes 57.8%, much better than the natural history, and a moderate improvement over the standard hypervolemic and hypertensive therapy. Nimodipine is probably safer, especially in preoperative cases.
Other drugs and techniques at various stages of trial, including cisternal perfusion, tissue plasminogen activator, aminosteroids and transluminal angioplasty, some of which have promising results, will be discussed.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

77 NIMODIPINE TREATMENT OF D.I.D. N. Dorsch. Dept of Neurosurgery, Westmead Hosp, Sydney, Australia.

Symptomatic vasospasm after SAH was treated with IV nimodipine. The first 141 cases included 100 females, and mean age was 50. The delay from the last SAH to ischemic symptoms was 1 to 16 days. Appropriate spasm was confirmed angiographically or by TCD in 123.

Treatment was started within three days of DID onset. Nimodipine was maintained at 30, or if needed 45ug/Kg/hr, and reduced over the last day or two. Duration of treatment was 1-27 days, mean 8.9. Side effects were minor and serious complications few. Hypotension occurred in 38 cases, but pressor support was needed in only six.

There were significant improvements in Hunt & Hess grade (at start of course 67 grade III, 59 IV, 15 V; at end 47 grade I, 14 II, 56 III, 15 IV, 9 grade V or dead), and in Glasgow Coma Score (33 on 14 or 15 at start, 99 at end). Overall, 119 improved. The final outcome was 105 good (Glasgow Outcome Score 1), 21 permanent deficits (eight GOS 2, 13 GOS 3), and 15 dead. Ischemia, alone or with other factors, accounted for only half the deaths.

These results are much better than the expected natural history (about 1/3 dead and 1/3 disabled), and a considerable improvement over fluid and hypertensive treatment (17% dead, 29% permanent deficits), calculated from a literature review. The treatment is also safer than induced hypertension, especially preoperatively.

78 DO COLLATERAL VESSELS PROVIDE PROTECTION IN VASOSPASM? N. Dorsch, Y. Zurynski. Depts of Neurosurgery and Intensive Care, Westmead Hospital, Sydney, Australia.

Patients with aneurysmal SAH had CBF (cerebral blood flow by 133-Xe clearance) and transcranial Doppler flow velocity (TCDV) measured. In 17 with delayed ischemic deficit (DID), TCDV rose to 139.0 cm/sec (SD 45). Six had a mean CBF below normal. In a second group of 15 similar results were obtained, but none had ischemic symptoms.

36 patients were treated with IV nimodipine for DID, and improved clinically. In 14, TCDV fell from an average of 142.8 to 89.4 cm/sec ($t = 3.6$, $P = 0.001$). CBF, studied before and after the start of nimodipine in six cases, increased significantly. The other 22 patients were similar clinically and in response to treatment, but their TCDV and CBF did not improve. In fact, the TCDV worsened significantly; in 13 cases studied both before and after nimodipine, it increased from 142.3 cm/sec, SD 44.5, to 180.6, SD 49,5; $t = 4.9$, $P = 0.0004$. The CBF fell in a few cases, but overall did not change greatly.

These results suggest that in some patients with severe vasospasm, CBF is maintained and ischemia does not develop, perhaps because of collateral vessels opening. Similarly, nimodipine in some cases appears to relax vessels in spasm, but in others must have a different mechanism, either the opening of collaterals or perhaps a direct neuronal protective effect.

79 RANDOMIZED COMPARISON OF TWO DOSES OF NICARDIPINE IN SUBARACHNOID HEMORRHAGE (SAH): PRELIMINARY REPORT OF THE COOPERATIVE ANEURYSM STUDY E.C. Haley, N.F. Kassell, J.C. Torner, and the Participants. Dept. of Neurosurgery, University of Virginia, Charlottesville, Virginia.

High dose intravenous nicardipine has been shown to reduce the incidence of angiographic and symptomatic vasospasm in aneurysmal SAH, but treatment may be complicated by side effects, including hypotension or pulmonary edema/azotemia. From 8/89 to 1/91, 365 patients were entered at 21 centers in a randomized, double-blind trial comparing high dose (0.15 mg/kg/hr) nicardipine with a lower dose (0.075 mg/kg/hr) administered by continuous IV infusion up to Day 14 following the SAH. Patients in all neurological grades were eligible.

During the study period, 184 patients were randomized to high dose nicardipine, while 181 were randomized to the low dose. There were no significant differences in age, admission neurological condition, or amount and distribution of blood clot on initial computerized tomography scan. Patients in the high dose group received a significantly smaller proportion of the planned dose ($80\pm0.2\%$ vs. $86\pm0.2\%$, $p<.05$), largely because of premature treatment termination due to adverse medical events. The incidence of symptomatic vasospasm was 31% in both groups, and the overall 3 month outcomes were nearly identical.

These data suggest that from a clinical standpoint, the results of high dose and low dose nicardipine treatment are virtually equivalent, but use of low dose nicardipine is attended by fewer side effects.

80 TCD-GUIDED TREATMENT WITH "HIGH-DOSE" NIMODIPINE FOR ESTABLISHED VASOSPASM AFTER ANEURYSMAL SAH S.C. Zygmunt, T.J. Delgado-Zygmunt. Department of Neurosurgery, University Hospital of Northern Sweden, S-901 85 Umeå, Sweden

The beneficial effects of treatment with calcium antagonists for prevention of the ischemic consequences of vasospasm following subarachnoid hemorrhage (SAH) have been presented in several controlled studies. Intravenous administration of nimodipine in dosages up to 3 mg/h have been used. The mechanisms behind the beneficial effects of nimodipine remain unclear. Both a direct vascular and cellular protective effect have been suggested.

In this study, using transcranial Doppler sonography (TCD), we evaluated the effect of intravenous nimodipine on cerebral vasospasm in aneurysmal SAH patients. Nimodipine treatment was initiated with 48 hours following SAH. The dosage was guided by the TCD findings; 1-2 mg/h was administered routinely. In the presence of vasospasm, the dosage was increased to up to 4 mg/h "high dose". Daily TCD measurements of flow velocities in ICA, MCA and ACA were performed.

Increasing nimodipine to 4 mg/h resulted in a reduction of the abnormally elevated flow velocities. In some patients, even a normalization of the values was obtained. An early reduction of nimodipine from 4 to 2 mg/h resulted in the return of abnormally elevated flow velocities.

In conclusion, an increase to "high dose" nimodipine treatment in patients with established vasospasm can result in normalization of flow velocities. TCD provides a useful tool for the guidance of individual treatment with nimodipine. Further studies are warranted to determine the optimal dose of nimodipine in the treatment of established vasospasm.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

81 A COMBINATION THERAPY OF NICARDIPINE INTRATHECALLY AND GLYCERYL TRINITRATE(GTN) INTRAVENOUSLY FOR PATIENTS WITH RUPTURED CEREBRAL ANEURYSMS

Y. Nishizawa, I. Saiki, M. Doi
Dept. Neurosurgery, Iwate Med. Univ., Morioka, 020 Japan

We will explain the efficacy of the combination therapy of intrathecally administered Ca antagonist(Nicardipine) in preventing vasospasm and GTN(nitroglycerin) in inducing dilatation of the contracted cerebral vessels for patients with ruptured cerebral aneurysms including severe cases. Subjects and Methods: From 209 patients who had under gone radical surgery within 48 hours after onset of ruptured cerebral aneurysm admitted into our department between Sept. 1989 and Mar. 1992, we selected 59 patients who received the combination therapy with 4mg x 2/day of nicardipine intrathecally and 1.5 to 5mg/h of GTN intravenously for 10 to 14 days postoperatively. The preoperative Hunt-Kosnik grades were II for 1, III for 15, IV for 12 and V for six. The Fischer CT grade were I for 1, II for 31, III for 10 and IV for 17. The mean age was 54.4 years, and period between onset and surgery was 17.3h in average. Results: (1)the ADL was 1 for 39 patients (66%), 2 for 9(15%), 3 for 7(12%), 4 for 3(5%) and 5 for 1(2%). (2) Symptomatic vasospasm was observed in 14 of 47 patients, except for those given thiopental sodium, however symptoms persists in only three patients(7%). (3) Four patients with poor ADL consisted of two with H-K grade of V, one with severe vasospasm, and another with a huge hematoma in the frontal lobe. (4) In 7 elderly patients with H-K grade III, the ADL was 2 for 1, 3 for 5 and 4 for 1, suggesting the problem of extended retention of the intrathecal drain. (5) For 6 patients with H-K grade V, ADL was 1 for 3(50%), 3 for 1 and 4 for 2, whereas for 12 patients with H-K grade IV, ADL was 1 for 6(50%), 2 for 5(42%) and 3 for 1. Conclusion: The incidence of symptomatic vasospasms was 7% in those patients receiving the combination therapy with Ca antagonist and GTN. The combination therapy produced a favourable prognosis, particularly in 78% of patients with severe SAH.

82 EXCELLENCE OF FLUNARIZINE AND FET TREATMENT ON DIND IN SEVERE SUBARACHNOID HEMORRHAGE

S. Fujita, T. Kawaguchi, and Y. Shose. Department of Neurosurgery, Hyogo Brain and Heart Center at Himeji, Himeji, Hyogo, Japan

A cerebral Ca^{2+} overload blocker-flunarizine hydrochloride(F)-was used with excellent results for prevention of delayed ischemic neurologic deficits (DIND) in severe SAH.

Of the consecutive 162 patients (90 Fisher's group III) including 82 FET (F plus Vit. E and Trifluoperazine-calmodulin antagonist-) treated orally with these drugs, only one in Fisher's group III developed DIND (1% of Fisher's group III). The cause of the DIND was attributable to administration failure of flunarizine. The association of severe angiographic vasospasm was less frequent (18%) in flunarizine treatment and even much less frequent (6%) with FET treatment. There were no side-effects from flunarizine, but one transient from trifluoperazine.

The results are extremely superior to those obtained in studies with nimodipine or nicardipine reporting that 10-30% of patients in Fisher's group III developed DIND and some of them died.

These highly benefical effects on delayed vasospasm might be attributable to better cerebral affinity and the strong cerebral protective effect of flunarizine, in combination with the anti-vasoconstrictive effect of trifluoperazine.

83 EFFECT OF A NEW POTENT AND LONG-ACTING CALCIUM ANTAGONIST, OPC-13340, ON EXPERIMENTAL VASOSPASM

T. Nakagomi, K. Yamakawa*, T. Sasaki*, and A. Tamura
Department of Neurosurgery, Teikyo University, *University of Tokyo, Tokyo, Japan

The purpose of this study was to evaluate the effect of a new potent and long-acting dihydropyridine calcium antagonist, OPC-13340, on experimental cerebral vasospasm. The canine "two hemmorrhage model" was used. To evaluate the magnitude of vasospasm, the diameter ratio was calculated as the percent of the basilar artery diameter of a given angiogram to that of its control. Mongrel dogs were divided into three groups. OPC-13340 was administered either intravenously (10 and 100 μg/Kg) or intrathecally 1 ml of 3 mM OPC-13340) 7 days following the first cisternal blood injection (Day 0). Significant basilar artery spasm was observed on Day 7 in each group. The diameter ratios were 53.9 ± 4.7 (mean ± SEM) % (10 μg/Kg, i.v.), 55.7 ± 4.0% (100 μg/Kg, i.v.), and 57.7 ± 3.8 % (3 mM, i.t.). Intravenous injection of OPC-13340 (10 μg/Kg or 100 μg/Kg) dilated the basilar artery significantly, and the diameter ratios were 56.9 ± 5.8 % (15 min following the injection, $p<0.05$) and 66.6 ± 3.5% (30 min, $p<0.01$) or 66.7 ± 6.0 % (15 min, $p<0.05$) and 72.3 ± 5.5% (30 min, $p<0.01$), respectively. Intrathecal injection of OPC-13340 (3 mM - 1 ml) also dilated the basilar artery significantly. The diameter ratios were 72.5 ± 3.7% (15 min following the injection, $p<0.01$), 83.9 ± 2.3 % (30 min, $p<0.01$) and 90.2 ± 2.8 % (90 min, $p<0.01$). These results indicate that OPC-13340 is effective in reversing cerebral vasospasm following subarachnoid hemorrhage.

84 CEREBRAL ANGIOPLASTY FOR VASOSPASM

Y.N. Zubkov, L.F. Alexander, G.M. Benashvili, R.R. Smith*. Polenov Neurosurgical Institute, St. Petersburg, Russia, and *Department of Neurosurgery, University of Mississippi Medical Center.

We report our results of treatment of 95 consecutive patients with radiographic and clinical confirmation of vasospasm. Constant monitoring and neuroleptanalgesia were used. Latex balloon catheters were introduced via the common carotid artery for anterior circulation spasm, and through the axillary artery for vertebrobasilar pathology. Dilatation was performed under fluoroscopic control.

In 85% of patients, angioplasty was performed on the fourth to fourteenth day after aneurysm rupture. Sixty percent of patients underwent dilation prior to direct clipping; 18% were treated postoperatively. Eight percent of patients underwent simultaneous angioplasty and detachable balloon occlusion of aneurysm. The indication for angioplasty was increasing hemispheric dysfunction with depressed level of consciousness in 66% of patients, and progressive hemiparesis in 34%. Fifty-six percent of patients were Hunt and Hess grade II at the time of treatment; 27% were grades IV or V.

Improvement of hemideficits, or amelioration of decreased level of consciousness, or both, was achieved in 83% of patients. Autopsy material revealed no arterial damage from dilation.

We feel that angioplasty deserves a prominent place in the neurosurgical treatment of vasospasm. Our protocol for the timing and implementation of angioplasty will be presented.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

85 DYNAMIC CEREBRAL BLOOD FLOW CHANGES BEFORE AND AFTER ANGIOPLASTY FOR VASOSPASM

Y.N. Zubkov, V.B. Semenjutin, Y. Tarassoli*. A.L. Polenov Neurosurgical Institute, St. Petersburg, Russia, and *University of Mississippi Medical Center, Jackson, MS.

This study consists of 26 patients who were investigated using xenon cerebral blood flow (CBF) techniques and 18 patients in whom hydrogen clearance blood flow methods were employed to evaluate cerebral vasospasm following an aneurysmal subarachnoid hemorrhage (SAH). These studies were carried out prior to angioplasty, in both symptomatic and asymptomatic patients encountered over the past 10 years at the Polenov Neurosurgical Institute in St. Petersburg. Xenon regional blood flow studies showed an irregular pattern in patients with cerebral vasospasm but blood flow was more significantly reduced in the territory supplied by the vasospastic artery to be treated. Regional blood flow was measured to a low point of 22 ml/100 gr/min in symptomatic patients.

Hydrogen clearance techniques were applied to two groups of patients. In one, angioplasty was carried out before aneurysmal clipping, and the other patients (who had evidence of cerebral vasospasm) underwent clipping without prior angioplasty. Angioplasty improved both blood flow and impedance. In the control group, CBF was significantly less than that of the patients who received angioplasty, and impedance significantly higher, representing cerebral edema.

These dynamic studies emphasize the improvements in the pathophysiology that may be obtained with early and prompt balloon vasodilatation in patients with cerebral vasospasm.

86 **ANGIOPLASTY FOR CEREBRAL VASOSPASM: FOLLOW-UP ON FIRST 50 CASES.**

M.R. Mayberg, J.M. Eskridge, D.W. Newell, H.R. Winn. *Department of Neurological Surgery, University of Washington, Seattle, WA. USA*

Transfemoral angioplasty is a new modality for the treatment of severe vasospasm refractory to conventional treatment. We report the results of 50 patients who received angioplasty at the University of Washington over the period from 1988 through 1992. An established protocol for all patients with subarachnoid hemorrhage (SAH) is utilized; including early surgery, intravascular volume expansion, calcium channel antagonists, intensive care and transcranial Doppler (TCD) monitoring. Among 445 patients with SAH treated at the University of Washington during this 4 year period, 50 (11%) developed delayed neurologic ischemic deficit attributable to cerebral vasospasm despite maximal medical therapy as above. Angioplasy produced a marked improvement in neurologic status (≥2 points on GCS scale) in approximately 70% of cases. Improvement in neurologic status correlated with TCD and SPECT measurements. Factors relating to success of angioplasty included duration of ischemia, location of spastic arterial segment, and co-existence of other intracranial lesions. The recent addition of intra-arterial papavarine infusion has allowed therapy for vessels inaccessible to the angioplasty catheter. Neurologic deterioration or death directly related to the angioplasty procedure occurred in 3 patients; unsecured aneurysms ruptured after angioplasty in 2 patients. Angioplasty is an effective and reasonably safe procedure for the treatment of vasospasm unresponsive to conventional therapy.

87 ANGIOPLASTY FOR CEREBRAL VASOSPASM - THE TORONTO HOSPITAL EXPERIENCE.

T.J. Coyne, W.J. Montanera, M.C. Wallace, R.L. Macdonald. Division of Neurosurgery, The Toronto Hospital, University of Toronto, Toronto. The Toronto Hospital experience with angioplasty for the management of post-subarachnoid haemorrhage vasospasm unresponsive to medical therapy was retrospectively reviewed. Thirteen patients in the three years to November 1992 were treated. The clinical manifestation of vasospasm was a decreased level of consciousness in 2, the onset of a focal deficit in 3, and both features in 8. The time from deterioration to angioplasty was an average of 18 hours (range 4-48, S.D. 13). Thirty-one vessels were dilated, 22 of these being in the anterior circulation. However, in 7 patients clinically relevant vessels, usually A1 or M2 vessels, were unable to be accessed and dilated. 6 patients had CT hypodensities at the time of angioplasty, with no complications. The majority of patients were in poor WFNS clinical grade prior to angioplasty (grade 3- 2 patients, grade 4- 7 patients, grade 5- 2 patients). Four patients (30%) showed an immediate improvement following the procedure. At 6 months following angioplasty, 5 (38%) were independent, 2 (15%) were alive but dependent, and 6 (46%) had died (5 from vasospasm, 1 from rebleeding from an incompletely treated aneurysm 14 days post angioplasty). There was a trend for worse outcome with worse clinical grade, though numbers were too few for statistical analysis.

This series has shown angioplasty to be safe, that it can be performed in the presence of CT hypodensities, and that it is efficacious in some patients. However, there were a number of poor outcomes, likely reflecting poor grade prior to the procedure, a relatively long interval from the onset of neurological deficit to angioplasty,and difficulty reaching A1 and M2 vessels. Angioplasty could have increased usefulness if these problems could be addressed.

88 PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY FOR SYMPTOMATIC VASOSPASM FOLLOWING SUBARACHNOID HEMORRHAGE

K. IRIE, Y. HONMA, H. KUYAMA, S. NAGAO. Dept. of Neurological Surgery, Kagawa Medical School, Kagawa, Japan

Recently percutaneous transluminal angioplasty (PTA) can offer an alternative therapy for management of cerebral vasospasm. PTA was performed on eight patients. To determine the best timing of PTA, mean flow velocity of the middle cerebral artery (MFV) was measured daily for 14 days following subarachnoid hemorrhage (SAH) with transcranial doppler ultrasonography (TCD) and cerebral blood flow (CBF) was measured with ^{99m}Tc-HMPAO single photon emission CT(SPECT) for 14 days after SAH. The indications for PTA at our institution are; 1) failure of a patient to respond to hyperdynamic therapy, with progressive clinical deterioration. 2) no evidence of infarction in the territory of spasm on CT scan. 3) a rapid increase in MFV above 120cm/sec. 4) the C/C ratio (cerebral hemisphere ROI counts/ cerebellar hemisphere ROI counts) calculated from SPECT images gradually decrease by less than 0.8. In 4 of 8 patients, PTA resulted in rapid improvements of consciousness and motor weakness. Neurologic improvements well correlated with abrupt decreases in MFV and increments of CBF. Outcome three months after SAH are as follows; good recovery: 4 cases, moderate disability: 1 case, severe disability: 1 case, dead: 2 cases. TCD and SPECT were useful to decide the timing of PTA and evaluate its efficacies. PTA is considered to be an effective treatment for symptomatic vasospasm when conservative therapy fails.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

89 TIMING OF INTRA-ARTERIAL INJECTION OF Ca^{++} ANTAGONIST (NICARDIPINE) AND PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY FOR VASOSPASM Y. Fujii, Y. Konishi, E. Sato, M. Hara, I. Saito. Department of Neurosurgery, Kyorin University School of Medicine, Mitaka, Tokyo, Japan

In the present study, we assessed the optimal timing of intravascular surgery by intra-arterial injection (IA) of Ca^{++} antagonist (nicardipine) and percutaneous transluminal angioplasty (PTA) for vasospasm following aneurysmal rupture. [Subjects and Methods] Our subjects consisted of 20 patients receiving IA of Ca^{++} antagonist (IA Group) with or without papaverine hydrochloride and 14 patients undergoing PTA (PTA Group). Cerebral angiography was performed within 24 hours after development of neurologic symptoms due to vasospasm (VS) and/or increased intracranial blood flow velocity on Transcranial Doppler Sonography (TCD). PTA was performed when VS was distributed mainly in the IC and M_1 portions, while IA was carried out in cases showing VS in the peripheral arteries. Injection of 5-10 mg of nicardipine was carried out through catheter inserted into C_5 portion of the carotid artery in 14 cases and 10-20 mg of papaverine hydrochroride was also admisistrated concomitantly in 8 cases in which dilatation of spastic arteries was not achieved. Timing of IA and PTA in these cases were assessed from the point of patients prognosis. [Results](1) The period between aneurysmal rupture and treatment was 6.6 ± 5.0 days for IA Group and 7.8 ± 2.1 days for PTA Group (NS). (2) 10 cases (55%) of IA Group and eight cases (60%) of PTA Group showed good prognosis, and there was no significant difference between the two groups. (3) Timing of treatment of patients was as follows: IA patients presenting with good prognosis was 4.0 ± 1.2days (n=6) and IA patients with poor prognosis was 9.8 ± 5.6 days (n=5)($p<0.05$); whereas PTA patients presenting with good prognosis was 7.0 ± 1.6 days(n=6) and PTA patients with poor prognosis was 9.0 ± 2.1 days (n=4)(NS). [Conclusion] Intravascular surgery for vasospasm may be effective with good prognosis, when IA is performed up to Day 4 and PTA is up to Day 7.

90 **Balloon angioplasty in the management of symptomatic vasospasm in patients with unclipped cerebral aneurysm**

T. Kataoka, T. Sasaki, T. Hyogo, J. Nakagawara, J. Nakamura, K. Suematsu
Department of Neurosurgery, Nakamura Memorial Hospital, Sapporo, Japan

introduction of balloon angioplasty (BAP) for the treatment of symptomatic vasospasm (VS) has raised new problems on the timing of the treatment in patients with unclipped aneurysm showing symptomatic VS. Which should be the initial treatment, aneurysm clipping or the BAP for the symptomatic VS? We discuss the timing and the indication of BAP in patients with unclipped aneurysm and symptomatic VS.

Two women and a man with ruptured aneurysm on day 10, 9, and 7 respectively, presented symptomatic VS on admission. Two of the 3 cases had CT evidence of recent re-rupture on admission. Xe-SPECT-CBF study was performed in all cases on admission for the estimation of severity of the cerebral ischemia due to severe VS. In one case with critical cerebral ischemia, 25 ml/100g/min on Xe-SPECT, we performed BAP prior to aneurysm surgery. In the other 2 cases showing the reduction of CBF, 35 and 27 ml respectively, we performed aneurysm surgery prior to BAP because of the recent evidence of re-rupture on CT.

We suggest that the presence of recent re-rupture and the severity of cerebral ischemia due to VS are important factors for deciding the initial management. Aneurysm surgery should be considered first in the case of recent re-rupture irrespective of CBF, whereas BAP should be considered first in the case of without re-rupture and critical CBF.

91 ANGIOPLASTY REARRANGES COLLAGEN AFTER SUBARACHNOID HEMORRHAGE R.R. Smith, Y.N. Zubkov, G.M. Benashvili, D.H. Bernanke**. Departments of Neurosurgery and Anatomy**, University of Mississippi Medical Center, Jackson, Mississippi; Polenov Neurosurgical Institute*, St. Petersburg, Russia.

Intracranial arterial vasospasm due to subarachnoid hemorrhage (SAH) remains a leading cause of morbidity and mortality from aneurysm rupture. The developmental mechanism of vasospasm and the effect of angioplasty also remain unknown.

In this study, we examined architecture of the intravascular collagen using SEM in patients with vasospasm before and after angioplasty. The arterial wall in spasm shows proliferation of connective tissue in the media and intima. There is good evidence that myofibroblasts increased the amount of collagen and its thickness. After angioplasty we found thinning of the arterial wall without disruption of cellular and connective tissue elements. Both were compressed and stretched. Damaged endothelium was not found. Efficacy of balloon angioplasty is due to compression and stretching of connective tissue which proliferated in the vessel after SAH. There may be some disruption at binding sites of the collagen fibril and myofibroblast.

92 HISTOLOGICAL STUDIES OF INTRACRANIAL VESSELS IN PRIMATES FOLLOWING TRANSLUMINAL ANGIOPLASTY FOR VASOSPASM. H. Kobayashi, H. Ide, H. Aradachi, Y. Arai, Y. Handa, T. Kubota
Department of Neurosurgery, Fukui Medical School, Fukui, Japan

The study was designed to observe morphological changes of intracranial vessels following transluminal angioplasty for cerebral vasospasm.

In 7 Japanese monkeys, cerebral vasospasm was induced by placement of autologous blood clot over major cerebral arteries. Angiography was performed on Day 0 and 7. The angioplasty was carried out for the right cerebral arteries with a silicone microballoon attached to a microcatheter on Day 7. The 3rd angiography was performed following angioplasty. The animals were sacrificed for scanning electron microscopy(SEM) and transmission electron microscopy(TEM).

SEM of the vasospastic arteries demonstrated endothelial convolutions covered with abnormal endothelial cells along the longitudinal axis. Areas with detached endothelium were observed in the vessels. TEM of the vasospastic arteries demonstrated marked corrugations of the internal elastic lamina, and endothelial cells compressed between tight folds of the elastic lamina. The degree of the endothelial cell damage resulting from the angioplasty was not so severe as that due to vasospasm itself. Most smooth muscle cells appeared intact following angioplasty.

Microballoon angioplasty for the treatment of cerebral vasospasm is a promising technique.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

93 Hemorheological and Hemodynamic Analysis of Hypervolemic Hemodilution Therapy for Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage K. Mori, H. Arai, M. Maeda. Department of Neurosurgery, Juntendo University Izunagaoka Hospital, Shizuoka 410-22 Japan

Between August 1990 and 1992, 73 early operations were performed on patients with ruptured intracranial aneurysms. Among them, 38 patients (52.1%) with clinical vasospasm were treated with hypervolemic hemodilution (H-H) therapy. Hct, Hb and the aggregation rate of RBC were measured daily day 1 to day 14. The quantitative measurement of CBF using ^{123}I-IMP and circulating blood volume (CBV) using ^{99m}T-HSA-D were periodically performed. The cardiac index and PCWP were also monitored through Swan-Ganz catheter. During H-H therapy, the Hct and Hb significantly decreased ($P<0.001$), accompanying with the 21.7% of decrease RBC aggregation rate. The CBV and CBF significantly increased during H-H therapy ($P<0.05$) comparing at the onset of clinical vasospasm. At the end of H-H therapy, 21 patients (55.3%) had become neurologically normal, 10 patients (26.3%) had mild or moderate disability, and 7 patients (18.4%) had severe disability or death. Death or severe disability from clinical vasospasm occured in 6.8% of all patients with SAH. Thus, we conclude that early surgery and aggressive managements of clinical vasospasm with H-H therapy can be accomplished with minimal morbidity.

94 COAGULOPATHY WITH THE USE OF HETASTARCH IN ANEURYSMAL VASOSPASM E.R. Trumble, J.P. Muizelaar, J.S. Myseros. Division of Neurosurgery, Medical College of Virginia, Richmond, Virginia 23298

The use of volume-expanding agents in post-SAH vasospasm has become the standard of care at many institutions. Risk profiles are necessary to ensure appropriate use of these agents. Hetastarch has been used at our institution in order to maximize cerebral blood flow (CBF) in post-aneurysmal SAH patients who are in vasospasm. In the course of our experience, we have noted multiple bleeding difficulties in those patients who have received hetastarch as a continuous intra-venous (IV) infusion. Therefore, a retrospective study was undertaken to assess indices that may be of assistance in preventing further occurrences of bleeding difficulties. Specifically, from 7/90-7/92, of the 78 patients who were admitted to the MCV neuroscience intensive care unit after clipping of an intra-cranial aneurysm, twelve experienced clinically significant vasospasm for which they received a hetastarch infusion as part of their therapy. A control group of five post-aneurysmal SAH patients in vasospasm received identical plasma protein fraction infusions. Three of the twelve hetastarch patients were noted to have clinically significant bleeding disorders requiring transfusions and, in one case, re-exploration. Of the indices studied, partial thromboplastin time (PTT) was found to be within normal limits prior to treatment but increased in all patients after treatment with hetastarch infusion, increasing from a mean of 24.5 to a mean of 33.6 ($p<0.002$). No bleeding difficulties or changes in indices were noted in controls. Hetastarch is shown to increase PTT in patients receiving an infusion. This finding is of import in dealing with the coagulopathic post-operative patient.

95 **SUPERSELECTIVE INTRA-ARTERIAL INFUSION OF PAPAVERINE FOR THE TREATMENT OF CEREBRAL VASOSPASM**

Y. Kaku*, Y. Yonekawa, T. Tsukahara, H. Yamada*

Department of Neurosurgery, National Cardiovascular Center, Osaka, Japan
*Department of Neurosurgery, Gifu University, Gifu, Japan

Introduction

The present report describes the successful treatment of cerebral vasospasm after subarachnoid hemorrhage (SAH) with superselective intra-arterial infusion of papaverine hydrochloride (PPV) and the experimental background of this treatment.

Measurement of Arterial responses *in vitro*

The arterial responses are measured by isometric tension method using ring segments of human cerebral arteries obtained from autopsy cases. Tsis *in vitro* experiment demonstrated that PPV is one of the most potent vasodilators of human cerebral arteries following SAH. PPV(10^{-4}M) induced submaximum vasodilatation to all of the control arteries and the arteries after SAH. This result suggested that PPV can be applied clinically as a vasodilator for the spastic arteries after SAH.

Clinical study

In a clinical study, fourty-one vascular territories in 12 patients were treated according to the following protocol. PTA was performed in two steps. A silicone balloon was used for dilatation of the internal carotid artery and the proximal MCA. A leak silicone balloon or Tracker 18 catheter was then introduced into or just proximal to the site of vasospasm not accessible to the angioplasty balloon catheter for superselective infusion of 0.2% PPV.

Result

Thirty-eight of 41 vascular territories were successfully dilated, and 10 of 12 patients showed improvement in neurological function after the procedure. There were no serious side effects due to infusion of PPV. It is essential to infuse PPV just proximal to the spastic vessels for delivering sufficient concentration, and PPV should be infused as early as possible before the artery loses the ability to return to normal luminal size.

Conclusion

Superselective intra-arterial infusion of PPV is an alternative method of treatment for symptomatic vasospasm.

96 THE TREATMENT OF CEREBRAL VASOSPASM AFTER SUBARACHNOID HEMORRHAGE WITH HIGH DOSE NICARDIPINE AND INTRA-ARTERIAL PAPAVERINE S.Yoshimura, Y.Yonekawa, T.Tsukahara, H.Miyake, A.Kobayashi, Y.Kaku. Department of Neurosurgery, National Cardiovascular Center, Suita, Osaka, Japan

We report the clinical effect of intravenous high dose nicardipine (5-10mg/Hr.) and percutaneous transluminal angioplasty (PTA) with superselective intra-arterial infusion of papaverine on symptomatic vasospasm after subarachnoid hemorrhage (SAH). Between August 1990 and September 1992, eighty-three SAH cases underwent early aneurysmal surgery, i.e., clipping of an aneurysm within day 2. Using cerebral hemodynamics followed by transcranial Doppler (TCD), we obtained reliable flow patterns in 46 cases from onset to day 14 everyday. Thirty three of 46 cases (72%) were treated with intravenous administration of high dose nicardipine (group I), and 13 cases (28%) were treated without calcium antagonists (group II). PTA with papaverine was performed in 9 cases (4 cases in group I and 5 cases in group II) of delayed ischemic neurological deficits not responding to conventional medical and pharmacological therapies such as hypervolemia and induced hypertension. Symptomatic vasospasm occurred in 6 of 33 cases (18%) in group I and 5 of 13 cases (39%) in group II. Average maximum mean flow velocity (MVF) was 96 ± 34 cm/sec in group I, and 96 ± 43 cm/sec in group II. Intravenous administration of high dose nicardipine reduced the incidence of symptomatic vasospasm, but did not change MFV of the major cerebral arteries. PTA with papaverine improved symptomatic vasospasm both clinically and angiographically in almost cases, and MVF of the major arteries immediately reduced. Morbidity of vasospasm was 3% in group I and 15% in group II, and mortality of vasospasm was 0% in each group. These results indicate that symptomatic vasospasm can be effectively treated by the combination of intravenous high dose nicardipine and PTA with papaverine.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

97 RESPONSE OF VASOSPASM TO INTRA-ARTERIAL INJECTION OF Ca^{++} ANTAGONIST (NICARDIPINE) Y. Fujii, Y. Konishi, E. Sato, M. Hara, I. Saito. Department of Neurosurgery, Kyorin University School of Medicine, Mitaka, Tokyo, Japan

In the present study, we assessed the effect of intra-arterial injection (IA) of Ca^{++} antagonist (nicardipine) to vasospasm following aneurysmal rupture.

Subject and Methods: This investigation was carread out as an open study on 22 patients. The average age of patients were 54.9 and all underwent early aneurysm surgery within 2 days after SAH. Cerebral angiography was performed within 24 houres after development of neurological symptoms due to vasospasm and/or increased intracranial blood flow velocity on transcranial Doppler sonography (TCD). Vasospasm was graded according to the degree of narrowing of main cerebral arteries compared with angiograms obtained before aneurysm surgery. Intra-arterial injection of Nicardipine (5~10mg) was carried out in 14 cases through a catheter inserted into C_5 portion of the carotid artery and papaverine hydrochroride (10~20mg) was also admisisrated concomitantly in 8 cases. Response of spastic arteries to Ca^{++} antagonist with or without Papaverine was assessed on angiograms obtained before and after drug injections. Results: Spastic arteries of less than 50% narrowing (17 cases) showed marked dilatation when IA was performed within 6 days after SAH. More severe vasospasm (5 cases) didnot respond enough to these drugs, and 4 of 5 cases with severe vasospasm showed neurological deterioration again later and they required balloon angioplasty 3 days after IA of drugs.

In conclusion, vasospasm of less than 50% narrowing showed good response to these chemical agents. More marked vasospasm, however, showed a slight temporary response and angioplasty was required later.

SESSION I
Vasospasm and the Timing of Aneurysm Surgery

98 TIMING OF ANEURYSM SURGERY AND ANGIOGRAPHY BASED ON TRANCRANIAL DOPPLER EVALUATION OF CEREBRAL VASOSPASM AND CLINICAL CONDITION.
Acerbi G.°,Pieri A.*,Caciagli P.*. °Division of Neurosurgery,Pescara Hospital, *Institute of Neuro surgery, Pisa University, Pisa, ITALY.
We report the results obtained in 63 consecutive aneurysm cases (12 ICA,18 MCA,22 AcoA, 4 ACA, 1 PICA,6 multiple) operated on by the senior Author (P Caciagli),following this protocol:CAT at admission and in case of clinical worsening;daily examination of cerebral basal arteries by a Transcranial Doppler (TCD)device (TC2-64,EME);cases with intracerebral hematoma and/or in grade IV-V of Hunt & Hess were excluded; in patients (p) admitted within 48 h after bleeding, angiography,early surgery (ES) and Nimodipine i.v.infusion, 2mg/h for 14days ;in p admitted more than 48 h after b,in absence of increased blood flow velocity of basal arteries (time-mean velocity less than 120 cm/sec) and in absence of TCD signs of increased intracranial pressure,treatment as the previous group,otherways Nimodipine i.v.infusion,angiography and surgery only after the critical phase of vasospasm development;At this time surgery is urgent in order to avoid the late rebleeding(Delayed-Urgent-Surgery, DUS).In 19 p the ES and in 44 the DUS policy was applied.The mortality rate was 10,5%in the ES and 0% in the DUS group.The results were excellent in 37,good in 20 and fair in 4 cases.Good results were achieved in 5p operated from day 4th to 10th after b.No cases of rebleeding verified in this series.

99 VASOSPASM AND THE TIMING OF SURGERY
Y.N. Zubkov, R.R. Smith*, L.F. Alexander*, G. Benashvili. A.L. Polenov Institute, St. Petersburg, Russia; Department of Neurosurgery*, University of Mississippi Medical Center, Jackson, Mississippi 39216-4505

Cerebral vasospasm, hydrocephalus, and rebleeding are found more often in patients with aneurysms in higher clinical grades. It is our belief that treatment of these altered pathophysiological states before operation can significantly improve overall outcome.

This study consists of 651 patients treated at the Polenov Neurosurgical Institute and the University of Mississippi Medical Center. This combined experience allows us to offer our system for management which we believe results in better clinical outcome. In our belief, emergency operation is indicated only in the presence of a space-occupying hematoma. In patients in good clinical grades, however, it is advisable to operate as soon as feasible. In higher clinical grades, grades III to V (subcompensated and decompensated), the complications responsible for decompensation must be managed prior to surgical clipping of the aneurysm. In compensated patients, vasospasm may be managed in either the asymptomatic or symptomatic phases prior to aneurysmal clipping. In subcompensated and decompensated patients, angioplasty must be performed prior to clip placement. In some cases, angioplasty for vasospasm may be combined with aneurysmal occlusion using endovascular methods. When ischemic deficits increase following clipping, angioplasty may also be performed postoperatively.

100 EFFECT OF SURGERY ON SEVERITY OF ANGIOGRAPHIC VASOSPASM. R.L. Macdonald, M.C. Wallace, T.J. Coyne. Division of Neurosurgery, University of Toronto, Toronto, Canada

Although early aneurysm surgery and clot removal may decrease vasospasm, evidence also suggests surgery worsens vasospasm. To quantify vasospasm, cerebral arterial diameters were measured on angiograms of 56 patients with aneurysmal subarachnoid hemorrhage (SAH). Angiograms were grouped by whether they were performed before or after surgery, and by time from SAH (0-2, 3-5, 6-8, 9-13, and ≥14 days). Aggressive surgical clot removal was not performed. Comparison of pre- and post-surgery angiograms at each time after SAH showed vasospasm was significantly greater on angiograms done post-operatively 3-5, 6-8, and 9-13 days after SAH ($p<0.05$, unpaired t-tests). Post-operative groups had more severe SAH on admission computed tomography (CT) scans. When a case-control method was used to match pre- and post-operative patients for CT grade of SAH, vasospasm was significantly worse in operated patients on days 3-5 and 6-8 ($p<0.05$, unpaired t-tests). Comparison between angiograms taken during vasospasm (days 3-13) for patients undergoing surgery before day 3, between days 3 and 13, and after day 13 showed vasospasm to be equal in groups undergoing surgery before day 13 and worse than on angiograms taken during vasospasm in patients operated after day 13. This difference persisted after matching for amount of blood on admission CT scan. Patients operated during days 3 to 13 were more likely to have cerebral infarction and poor outcome. Results of this retrospective review suggest that surgery may aggravate vasospasm, particularly when carried out 3 to 13 days after SAH.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

101 TEMPORARY CLIPPING IN EARLY ANEURYSM SURGERY AFTER SAH - INFLUENCE ON VASOSPASM AND CLINICAL OUTCOME B. Meyer, K. Schaller, V. Rohde, W. Hassler. Department of Neurosurgery, Klinikum Kalkweg, Duisburg, Germany

Temporary clipping during aneurysm surgery produces, even within the "safe" time limit of 15 min (Ojeman 1988), inevitably endothelial damage. Aim of this study was to show the influence on cerebral vasospasm and late clinical outcome. We therefore analysed the data of 64 patients that were operated early (<72H) after SAH in 1990 (47 f, 17 m, mean age 45.2 y). Late follow up was performed in all patients 1 year after the operation. *Group 1* comprised 42 patients without temporary clipping during aneurysm surgery. *Group 2* included 22 patients where temporary clips were used (4 for premature rupture, 18 during aneurysm perparation). Risk factors regarding vasospasm and clinical outcome were evenly distributed among both groups (Hunt and Hess grades, Fisher grades, minor leaks...). Our results showed no difference for the incidence of severe vasospasm on TCD (42% in group 1, 41% in group 2). Group 2 however showed a higher ratio of delayed ischemic neurological deficit (DIND) with 45% versus 32% in group 1. Increased blood flow velocities on TCD at the time of late follow up were also evenly distributed among both groups (group 1: 16%, group 2: 15%). Clinical outcome at that time however was significantly different. 47% of all patients in group 2 had only a fair/poor outcome. In group 1 only 30% were found in those low categories. We could not find a correlation between fair/poor outcome and clipping time or premature rupture in group 2. But it was correlated to the presence of vessel anomalies and surgery of aneurysms in the anterior circulation. In contract to other reports we therefore conclude that temporary clipping does not necessarily lead to a higher incidence of severe vasospasm in TCD, but does have a negative influence on the clinical outcome. Especially patients with anomalies (hypo-/aplasia) and aneurysms of the anterior circulation should not be candidates for temporary clipping.

103 POST-TRAUMATIC VASOSPASM INFLUENCES HEAD INJURY OUTCOME. N. Dorsch, Y. Zurynski. Department of Neurosurgery and Intensive Care Unit, Westmead Hospital, Westmead NSW 2145, Australia.

Post-traumatic vasospasm (PTV) is common after severe head injury and may cause secondary damage, but deterioration is difficult to assess in deeply sedated patients. We have correlated the incidence of vasospasm with outcome. Thirty severely head injured (GCS < 8) patients were studied. All were ventilated, sedated and undergoing intracranial pressure monitoring. Transcranial Doppler ultrasound blood flow velocities (TCDV) were monitored in middle and anterior cerebral, basilar and the extracranial internal carotid arteries. Intracranial TCDV 100cm/s or more for at least 24 hours, with normal or low extracranial velocities, were considered to show PTV. Outcome was assessed six months after injury using the Glasgow Outcome Scale (GOS) and the Disability Rating Scale (DRS).

Seventeen out of 30 patients developed PTV. Patients with PTV had a significantly longer stay in the intensive care unit ($p < 0.01$) and scored significantly worse on the GOS ($p < 0.05$) and the DRS ($p < 0.01$). There was also a significant correlation (rank-order) between the highest TCD velocity and GOS ($r=0.38$, $p < 0.05$) and DRS ($r=0.48$, $p < 0.01$).

This study suggests that severe head injury can lead to PTV, and that it has a detrimental effect on outcome. These findings have implications for routine monitoring and treatment of vasospasm in head injury.

SESSION J
Vasospasm – Other Aspects

102 VASOSPASM FOLLOWING CEREBRAL MENINGITIS ? - A TCD STUDY:
H.-P.Haring, H.K.Rötzer, A.Kampfl, B.Pfausler, K.Berek, E.Schmutzhard. Department of Neurology, Univ. of Innsbruck,A-6020 Innsbruck,Austria.

In a three year period 110 patients with CNS infections of various etiology were examined serially by means of TCD.

Transtemporally blood flow velocity (v-mean) of the M1-segment was investigated on a daily basis. A mobile TCD-equipment with a 2 MHz probe was used.

In viral induced infections no changes of flow velocity in basal cerebral arteries were seen whereas in bacterial meningitis a significant increase of blood flow velocity in the MCA was recorded (Student's t - test $p < 0,05$). Its extent was mainly associated with the type of the infectious agent, most frequently observed in pneumococcal meningitis (77%). The increase was up to 100% of the baseline values and was reversible in all cases.

Our results clearly underline that similar hemodynamic changes as known from SAH may be observed in bacterial meningitis too. An underlying inflammation of cerebral vessel walls seems to be the main pathogenic mechanism.

104 EFFECT OF NIMODIPINE ON CEREBRAL BLOOD FLOW VELOCITY AND OUTCOME IN SEVERE HEAD INJURY PATIENTS R.W. Seiler, U. Gröger, H.J. Steiger, R. Stooss. Division of Neurosurgery, University of Berne, CH-3010 Berne, Switzerland

Background and purpose: Vasospasm and secondary ischemia also occurs after head injury. We evaluated the effect of Nimodipine on cerebral blood flow velocities and outcome after severe head injury.

Methods: In a double blind, placebo-controlled study, 86 patients with severe head injury (GCS <10) were treated with Nimodipine 2 mg/h i.v. for 7 days. ABP, ICP, pCO_2 and hemoglobine were recorded routinely and all patients had sequential transcranial Doppler investigations of both MCA's and ICA's. The CT's were graded for intracranial blood after the classification of Fisher.

Results: There was no statistically significant difference in GCS, CPP, CT-grade and hemoglobine between the two groups. Flow velocities of the ICA's were identical, but the flow velocities of the MCA's were significantly lower ($p=0.05$) in the Nimodipine group. There was no difference in outcome.

Conclusion: Nimodipine reduced significantly the blood flow velocity of the MCA's but had no effect on outcome.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

105 CBF AND PREDICTION OF POST-TRAUMATIC VASOSPASM N. Dorsch, Y. Zurynski, I. Pearson. Department of Neurosurgery and the Intensive Care Unit, Westmead Hospital, Westmead NSW 2145, Australia.

Although post-traumatic vasospasm (PTV) has been reported to occur after severe head injury and cause secondary injury, prediction is difficult. Early measurement of CBF is an accurate predictor of vasospasm after aneurysmal SAH(1), and we assess here the usefulness of CBF and CT in predicting PTV.

Transcranial Doppler ultrasound (TCD) velocities were measured in 45 severely head injured (GCS < 8) patients. The major cerebral arteries and extracranial internal carotids were assessed within 24 hours, then daily. Xenon-133 cerebral blood flow (CBF) was measured within 24 hours of injury in 34 patients. The amount of subarachnoid or subdural blood on CT was also assessed in relation to future PTV. The CBF initial slope index (ISI) values for patients who did not develop vasospasm fell predominantly between 30 and 43. Patients whose ISI fell on either side of this range had a significantly higher chance of developing PTV (χ^2 = 10; p = 0.002, odds ratio 18). PTV was predicted with 87.5% sensitivity, 77.8% specificity and 82.4% accuracy. This was much more accurate than CT. These results suggest that accurate prediction can be obtained from CBF measurements taken within 24 hours of injury. Further study is needed to test these predictive values prospectively. 1. Dorsch N.W. Zurynski Y. J Cereb Blood Flow Metab 1987, 7(Suppl 1):649.

106 NATRIURETIC PEPTIDES AND ANTIDIURETIC HORMONE FOLLOWING SUBARACHNOID HEMORRHAGE E. Isotani, R. Suzuki, K. Tomita, M. Hokari, S. Monma, K. Hirakawa, F. Marumo. Department of Neurosurgery, and the second Department of Internal Medicine, Tokyo Medical and Dental University, Tokyo, Japan

Purposes : In this study, we investigated whether changes are seen in serum natriuretic peptides and antidiuretic hormone (ADH) levels after SAH.

Subjects and Methods : Among twenty two patients with verified SAH admitted to our department, fourteen patients show hyponatremia (serum Na ≦ 135) during their clinical courses. Samples were taken from day 0 to day 14. Brain natriuretic peptide-like immunoreactivity (BNP-LI), atrial natriuretic peptide-like immunoreactivity (ANP-LI) and ADH were measured radio-immunologically.

Results : Normal BNP-LI level was 0 to 6 pg/ml. Mean plasma BNP-LI levels were 19.5 (14.5 SD) on day 0 to 2, 12.3 (21.1) on day 6 to 9, 11.5 (20.2) on day 12 to 14. Normal ANP-LI level was 10.0 to 60.0 pg/ml. Mean plasma ANP-LI levels were 68.0 (18.1), 54.9 (16.4), 55.1 (16.2). Normal ADH level was 0 to 6 pg/ml. Mean plasma ADH levels were 12.6 (16.6), 2.0 (1.5), 2.2 (1.4). No definite correlations were found between hyponatremia and these peptides. But in some hyponatremic patients, relatively high titers of natriuretic peptides continued, though did'nt ADH.

Conclusions : Various peptides levels are elevated in systemic blood circulation after SAH.

107 PHASE TWO TRIAL OF TIRILAZAD IN ANEURYSMAL SUBARACHNOID HEMORRHAGE N.F. Kassell, E. Clarke Haley, W.M. Alves, C. Apperson Hunsen, B. Weir and the Participants. Department of Neurosurgery, University of Virginia

Tirilazad mesylate is effective in preventing vasospasm and decreasing infarction in animal models, making it a theoretically attractive agent for patients with ruptured aneurysms. In a Phase II double-blinded, dose-esculating safety trial, 245 patients from 12 Canadian centers were enrolled and treated within 72 hours of SAH with nimodipine alone, 60 mg every four hours p.o. for up to 21 days, (vehicle), or with nimodipine plus tirilazad, I.V. (0.6 mg/kg per day group, 2.0 mg/kg per day group, or 6.0 mg/kg per day group) for ten days post bleed.

In these patients, there were no serious adverse medical events thought to be related to the use of tirilazad. For all categories of medical events, there were no statistically significant differences in incidence rates between the vehicle and active drug tested groups. In the 0.6 and 2.0 mg/kg per day doses, symptomatic vasospasm was reduced and favorable outcome was improved in a dose-related manner comparable to the vehicle. The differences were noted between the vehicle group and the 6.0 mg/kg per day tirilazad group.

This study demonstrates that tirilazad is safe in patients with ruptured aneurysm in doses up to 6.0 mg/kg per day for up to ten days following subarachnoid hemorrhage. Furthermore, it suggests that this agent is effective in reducing symptomatic vasospasm and improving outcome after aneurysmal SAH. Two large-scale efficacy studies are underway to confirm these findings.

108 **U78517F TREATMENT AFTER EXPERIMENTAL SAH: EFFECTS ON LIPID PEROXIDATIVE PATTERNS IN SYNAPTOSOMAL CORTICAL PREPARATIONS** P.Gaetani, F.Marzatico*, C.Café*, A.L.Messina and R.Rodriguez y Baena
Department of Surgery, Neurosurgery, IRCCS Policlinico S.Matteo and *Institute of Pharmacology, University of Pavia, Italy

Recently, the new non-steroidal lazaroid (U78517F) combining the characteristics of 21-aminosteroids with the anti-oxidant properties of vitamine E has shown a 10-fold greater anti-lipid peroxidative effect in experimental cerebral ischemia. In the present study we have tested the effects of U78517F in an experimental model of SAH (autologous arterial blood injection into cisterna magna of Sprague-Dawley rats) with regards to lipid peroxidative patterns of synaptosomal cortical preparation. The animals were divided into the following groups: (a) sham-operated (SO); (b) hemorrhagic (SAH); (c) SAH-treated (SAH+T) rats subjected to SAH procedure and treated with U78517F, 5 mg/Kg i.v. immediately after surgical procedure. The animal of three groups were killed after 24 hrs after surgical procedure. The biochemical evaluation were performed on synaptosomes in a basal condition and after 1,3,5,10 and 20 minutes of lipid peroxidation stimulation with Fe++ and ascorbic acid.

5' nucleotidase (5'ND) (plasma membrane marker): no changes can be detected in this activity, neither following SAH or during stimulation of lipid peroxidation, indicating that 5'ND activity is unsensitive to peroxidative stress. No changes were registered subsequently to U78517F administration.

Na-K ATPase (ATPase) (marker of integrity of nerve endings and membrane-dependent vital synaptic functions) decreases since 1 min of stimulatio with the peroxidative mixture. No significative differences can be seen between SO and SAH; the trated group shows a trend towards higher values of ATPase activity than SAH group.

TBARS (thiobarbituric acid reactive substance): the values significantly increase since 3 min in the sham-operated group, already at the 1st min in the SAH group and only at the 10th min in the treated group, indicating a greater resistance of the synaptosomal membranes in the rats treated with U78517F.

Furthermore at 3 and 5 min of stimulation of lipid peroxidation the TBARS values of the hemorragic group are significatively higher than those of the SO and treated groups, supporting the evidence of a protective action of the drug on membranes. The results of the study indicate that the lipid peroxidation measured as TBARS *does not correlate with ATPase activity measured in the same conditions and that* U78517F treatment could exert a protective role on synaptosomal fractions against lipid peroxidative reactions.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

109 **EFFECTS OF THE DUAL ACTION COMPOUNDS, U92032 AND U92798, ON EXPERIMENTAL CEREBRAL VASOSPASM IN RABBIT.**

Shuhei Takahashi, Neal F. Kassell, Katsunobu Takenaka, Toshiki Aoki, Kevin S. Lee. Department of Neurological Surgery, University of Virginia, Charlottesville, VA 22908

U92032 and U92798 are recently-developed, tropolone derivatives which inhibit lipid peroxidation and act as calcium antagonists. **[Materials and Methods]** The effects of U92032 and U92798 on basilar artery tone were examined in two model systems: 1) an in vitro preparation of arterial rings which measures isometric tension and, 2) an in vivo model of cerebral vasospasm measuring arterial diameter. **[In Vitro Measurements of Basilar Arterial Rings]** U92032 and U92798 (10^{-8} to 10^{-5} M) elicited a dose-dependent relaxation of arterial rings preconstricted with elevated potassium (KCl; 40mM), endothelin-1 (ET-1; 10^{-8}M), or phorbol 12,13-dibutylate (PDB: 10^{-7}M). Dose-dependent relaxing effects of U92032 and U92798 on KCl-induced contractions were observed in the presence of calcium concentrations ranging from 0.01 to 20 mM. The relaxing effect of U92032 was slightly more potent than that of U92798. **[Morphometric Studies of Basilar Arteries following Subarachnoid Hemorrhage]** Vasospasm of basilar arteries following subarachnoid hemorrhage was inhibited by U92032 and U92798. Intravenous injections of U92032 and U92798 attenuated spastic constrictions (0.1-1.0 mg/kg). **[Conclusion]** The dual actions of U92032 and U92798, i.e. blocking calcium entry and inhibiting lipid peroxidation, make it an attractive candidate for treating vascular pathology. The current findings suggest that compounds of these types may be useful in the prevention of cerebral vasospasm following subarachnoid hemorrhage.

110 PROTECTIVE EFFECT OF U-78157F ON LOCAL CEREBRAL GLUCOSE UTILIZATION IN THE ACUTE STAGE FOLLOWING SUBARACHNOID HEMORRHAGE (SAH).

D.d'Avella*, M.Zuccarello**, F.Tomasello*
Departments of Neurosurgery *University of Messina, Italy, and **University of Cincinnati, Ohio, USA

This study investigates the effect of a 2-methylaminochroman (U-78157F), novel inhibitor of lipid peroxidation on the SAH-induced cerebral hypometabolism. SAH was induced in rats by direct injection of 0.3 ml of autologous, non-heparinized arterial blood into the cisterna magna. Animals were divided into four experimental groups: 1) Sham-operated rats (n=6), 2) Mock cerebrospinal fluid (CSF) injection (n=6), 3) SAH rats (n=6), and 4) SAH rats treated with 2mg/Kg of U-78157F 15 min prior to and 1 h after SAH (n=6). Three hours after the beginning of each experiment all animals received intravenous injection of [^{14}C]2-deoxyglucose. Local cerebral glucose utilization (LCGU) rates were determined by quantitative autoradiography. In comparison with sham- and mock CSF-operated rats, LCGU was diffusely decreased following SAH. Statistically significant decreases in metabolic activity of ≤40% were observed in all brain regions studied. Subarachnoid injections of mock CSF also induced a decrease in LCGU, but the changes were not as great as those found in SAH rats. The treatment with U-78157F significantly prevented metabolic suppression after SAH in all region studied, even though the levels of LCGU always remained below those found in sham-operated rats. Our study supports the beneficial effect of 2-methylaminochromans following SAH.

111 INTRAVENOUS FUT-175 INHIBITS COMPLEMENT ACTIVATION IN THE CEREBROSPINAL FLUID AND VASOSPASM-RELATED DELAYED ISCHEMIC NEUROLOGICAL DEFICIT FOLLOWING SUBARACHNOID HEMORRHAGE

H. Yanamoto[1], H. Kikuchi[1], S. Okamoto[2], J. Ishikawa[3], M. Matsumoto[2], Y. Shimizu[4], M, Sato[4], Y. Tokuriki[5], K. Matsumoto[5], M. Nakamura[6] Department of Neurosurgery, Kyoto University Medical School[1], Department of Neurosurgery, Osaka Red Cross Hospital[2], Department of Neurosurgery, Maizuru Municipal Hospital[3], Department of Neurosurgery, Shimizu Hospital[4], Department of Neurosurgery, Fukui Red Cross Hospital[5], Research Laboratories, Torii & Co., Ltd.[6]

The possible role of complement activation in the development of cerebral vasospasm following subarachnoid hemorrhage (SAH) was investigated. C3a, C4a, and SC5b-9 levels were monitored in the cerebrospinal fluid (CSF) of patients for seven days after the onset of acute SAH. Plasma C3a and C4a levels were also monitored. In addition, the serine protease inhibitor FUT-175 was intravenously administered to ten randomized consecutive patients in the acute phase following severe SAH. This inhibitor has previously been reported to prevent cerebral vasospasm.

C3a and SC5b-9 CSF levels were both elevated in the acute phase of severe SAH. The elevation was significantly greater on day 1 in patients with SAH complicated by vasospasm-related delayed ischemic neurological deficit (DIND) than in patients without DIND. The ten FUT-175-treated patients did not develop DIND, and their CSF C3a and SC5b-9 levels were significantly lower than those of the untreated patients who developed DIND.

The correlation of CSF C3a and SC5b-9 activation with the development of DIND strongly suggests that complement activation plays a role in the development of cerebral vasospasm after SAH. Inhibition of complement activation by FUT-175 appears to prevent the development of cerebral vasospasm and subsequent DIND.

112 THERAPEUTIC EFFECT OF A NEW IMMUNOSUPPRESSANT FK-506 ON VASOSPASM AFTER SUBARACHNOID HEMORRHAGE

S. Nishizawa, J.W. Peterson, I. Shimoyama, K. Iwasaki, T. Yokoyama, H. Ryu, K. Uemura. Department of Neurosurgery, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan and Laboratory for Cerebrovascular Biophysics, Massachusetts General Hospital, Boston, Massachusetts, USA

The authors had reported the efficacy of an immunosuppressant, cyclosporine for prevention of vasospasm after subarachnoid hemorrhage (SAH). To investigate further mechanism of immunological process in the development of vasospasm, we examined therapeutic effects of a new immunosuppressant, FK-506 on vasospasm in the animal model.

Forty dogs were randomly classified into four groups :sham, SAH, treat-1(FK-506, 0.3mg/Kg/day), and treat-2(0.15mg/Kg/day). Angiographical extent of vasospasm, serum C3 and CH50 values were evaluated. In treat groups, serum levels of FK-506 were also monitored.

As for the extent of vasospasm, the difference between sham and other three groups was statistically significant. However, no difference among SAH, treat-1 and treat-2 was noted. No difference in C3 or CH50 level among four groups was noted, either.

These results indicate no therapeutic efficacy of FK-506 on vasospasm. The different immunosuppressive mechanism in situ between cyclosporine and FK-506 would lead to a complete different result. This difference suggests that the immunological response which is suppressed by cyclosporine might play a pivotal role in the development of vasospasm, although the response suppressed by FK-506 might not.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

113 BOTH CYCLOSPORINE A AND FK-506 FAILED TO PREVENT CEREBRAL VASOSPASM IN CANINE TWO HEMORRHAGE MODEL

K. Nagata*1, T. Sasaki*2, T. Mori*3, H. Ooami, H. Nirei*4, K. Hamada, T. Kirino*2. *1Dept of Neurosurgery, New Tokyo Hospital, Matsudo, Chiba, *2Dept of Neurosurgery, University of Tokyo, Bunkyo-ku, Tokyo, *3Division of Pathology, Institute of Gerontology, Nippon Medical School, Kawasaki, Kanagawa, *4Expl Res Labo, Fujisawa Pharmaceutical Co. Ltd., Tsukuba, Ibaraki, Japan

In order to clarify the possible role of immunological reaction in the pathogenesis of cerebral vasospasm(VS), we examined the prophylactic effect of immunosuppressants, FK-506 and cyclosporine A(CSA), using canine two hemorrhage model. While the basilar artery constricted up to 81.0±4.0 % on day 2 and 63.8±3.5 % on day 7 in the non-treated group, it also constricted to 77.9±3.4, 62.8±3.0 % respectively in FK-506 group (N.S.). This constriction was also observed in CSA treated group, and the basilar artery constricted to 81.8±3.7 % and 56.3±2.7 % respectively (N.S.). The histological examination, including immunohistochemical study, could not discriminate the differences among these group. Since these immunosuppressants show their effect mainly through the inhibition of interleukin 2 (IL-2), we examined the level of IL-2 in the cerebrospinal fluid of clinical patients with cerebral vasospasm. While IL-1 gradually increased in level as time passed, the level of IL-2 was constantly low during the course of study, indicating the less participation of IL-2 in the pathogenesis of VS. This clinical observation was well matched to our experimental results. These results suggest that cell-mediated immunoreaction, initiated mainly by IL-2, plays little role in the pathogenesis of VS.

114 COMPLEMENT-INDUCED LYSIS OF SUBARACHNOID ERYTHROCYTES MEASURED DURING DEVELOPMENT OF CEREBRAL VASOSPASM

J. Peterson, R. Sibilia, M. Kaoutzanis, K. Yamakawa, N.T. Zervas Neurosurgical Service Massachusetts General Hospital, Boston, MA

The hypothesis that RBC's trapped in subarachnoid(SA) clot become progressively immunoreactive and subject to lysis by serum complement has been investigated in the canine model by introducing purified 125-I labeled canine complement proteins C5 or C8 at various times during the development of vasospasm. Allowing 20-24 hr for possible extravasation and incorporation of complement into the "membrane attack complex (MAC)" on SA RBC membranes, the brain was then fixed in situ and excised. Pieces of clot were weighed and counted for 125-I protein, then washed repeatedly in hypotonic buffer to remove trapped/lightly bound counts. Wash solutions were assayed for Hgb as a normalizing factor for clot sample size. Washed pellets of RBC membranes were counted for complement protein incorporation. A quantitative relation between membrane-bound 125-I and RBC lysis was established by in vitro measurements of label incorporated during the lysis of xenologous RBC's by plasma prepared from the labeled dogs.

To date, we find that extravsation and incorporation of 125-I labeled C5 and C8 (core proteins of MAC) is significant. During the later stages of vasospasm, sufficient label was incorporated into the membranes of SA RBC's to account for 12% to 24% lysis in the SA clot (n=3) in 24 hours.

115 PREVENTION OF CEREBRAL VASOSPASM BY MEANS OF INTRATHECAL FIBRINOLYTIC THERAPY WITH TISSUE-TYPE PLASMINOGEN ACTIVATOR

K. Mizoi, T. Yoshimoto, A. Takahashi, K. Koshu
Division of Neurosurgery, Tohoku University School of Medicine, Department of Neurosurgery, Kohnan Hospital, Sendai, Japan

We have evaluated the efficacy of postoperative intrathecal injection therapy of tissue-type plasminogen activator (tPA) in preventing cerebral vasospasm in cases with a diffuse thick subarachnoid hemorrhage. The present study examined the 44 cases that underwent direct surgery within 48 hours of onset and whose computerized tomography (CT) findings were classified as Fisher's Group 3. All 44 patients showed diffuse thick subarachnoid blood clots with CT numbers greater than 75. After aneurysm clipping and clot removal, three cisternal drainage catheters were inserted into the bilateral sylvian fissures and the prepontine cistern, respectively. On the day following the operation, tPA (2 mg) was infused to each cisterns, and this was continued for several days until all of the cisterns became low density in CT scans. Follow-up angiography showed that 38 cases (86%) had no vasospasm, 5 had moderate vasospasm (11%) and 1 had severe vasospasm (2%). All six patients showing angiographical spasm were however asymptomatic. There was one case with a complication of subarachnoid hemorrhage caused by drainage catheter removal, two small epidural hematoma and three subgaleal fluid accumulation, all of which were treated conservatively with favorable results. Overall, there were no infectious complications related to intrathecal injection therapy with tPA. These results indicate that intrathecal multiple injections of small doses of tPA are effective and safe in preventing vasospasm. On the basis of our experiences thus far, we conclude that injection of 2 mg of tPA daily for 5 days (a total of 10 mg) is effective in preventing the development of vasospasm.

116 Early phase II clinical trial of intrathecal rt-PA(TD-2061) for the prevention of cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage.

T. Sasaki, T. Ohta, H. Kikuchi, K. Takakura, M. Usui, H. Ohnishi, A. Kondoh, H. Tanabe, J. Nakamura, K. Yamada. TD-2061 Cooperative Study Group in Japan

The results of early phase II trial (a multicenter, open, dose escalation study) of intrathecal rt-PA for the prevention of cerebral vasospasm were reported. Fifty three patients admitted within 48 hrs of SAH were enrolled in this study. All cases enrolled were classified in clinical Grade II, III or IV (Hunt and Kosnik) and in Group 3 or 4 (Fisher's CT grading scale). Surgery for clipping the aneurysms was performed and a small silicone catheter was left in the subarachnoid space. Twenty four hours after the surgery intrathecal bolus infusion of rt-PA was started through the silion catheter at 8-hr intervals for 5 days. Patients were divided into 3 groups based on the dosage of rt-PA for each injection. The dosage of rt-PA for each injection and number of cases in each group was as follows: 50 KIU in 16 cases, 100 KIU in 17 cases and 200 KIU in 20 cases.

There was no significant difference both in the clearance of subarachnoid clots and in the occurrence of angiographic vasospasm between three groups. However, the occurrence of symptomatic vasospasm was less in the 200 KIU group than in other two groups. Intracranial bleeding complications were noted in 4 patients.

These results suggest that intrathecal administration of 50-200 KIU of rt-PA at 8-hr intervals for 5 days is effective in preventing the occurrence of vasospasm.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

117 THE RELEVANCE OF THROMBOLYTIC THERAPY FOR THE PREVENTION OF VASOSPASM. IN VITRO AND CLINICAL STUDIES K. Kanamaru, S. Waga. Department of Neurosurgery, Mie University School of Medicine, Tsu, Mie 514, Japan

The rt-PA has been effective in prevention of cerebral vasospasm after subarachnoid hemorrhage (SAH). It seems still unclear until when rt-PA can effectively resolve the clots after SAH, because the plasminogen in the clots may be decayed during first week of SAH. In the in vitro study, the effect of rt-PA on the clot lysis was investigated at 1, 3, 6, 12, 24, 48, 72 and 96 hours after clot formation. The rt-PA resolved the clots almost completely in 1, 3 and 6 hours groups. In electron microscopy of the clots, the morphological change of red blood cells was noted in 48 hours group. In 96 hours group, cell membrane was disrupted and hemolysis was observed. Furthermore, the clots from this group enhanced the contraction induced by prostaglandin F2α in the isolated canine basilar artery. In clinical study, intraoperative thrombolytic therapy was performed in 26 patients within 48 hours of SAH. Delayed neurological deficit due to vasospasm was significantly less frequent in rt-PA (T) group than simple cisternal drainage (D) group ($P<0.01$). According to Glasgow Outcome Scale, T group had a significantly better outcome than D group ($P<0.01$). These results suggest that rt-PA is effective in reducing vasospasm and improving outcome of the patients if this treatment is started within 48 hours of SAH.

118 COMPARATIVE STUDY OF CISTERNAL LAVAGE METHODS FOR THE TREATMENT OF CEREBRAL VASOSPASM K. Kanamaru, S. Waga, M. Sakakura, A. Morikawa, Y. Yamamoto, Y. Morooka, M. Okada. Department of Neurosurgery, Mie University School of Medicine, Tsu, Mie 514, Japan

We attempted to compare the clinical efficacy of four modalities evacuating clots from basal cisterns as following: simple cisternal drainage (D, N=37); ventricular or cisternal irrigation combined with cisternal drainage (I, 13); cisternal urokinase irrigation with cisternal drainage (U, 25); and single intracisternal injection of recombinant tissue type plasminogen activator (rt-PA) with cisternal drainage (T, 29). The patients undergoing surgery within 48 hours of aneurysm rupture were assigned into four groups. The incidence of delayed neurological deficit was 40.5% (N=15) in D, 23.1 (3) in I, 32.0 (8) in U, and 17.2 (5) in T groups. There was a statistical significant difference between D and T groups ($P<0.01$). However, there was no significant difference between other groups. According to Glasgow Outcome Scale, the percentage of the patients included in good outcome was the same in each group (I;N=6, 46.2%, U;12, 48.0, T;14, 48.2, D;17, 45.9). Moderate and severe disability was less common in U and T than I and D groups (I;N=5, 38.5%, U;4, 16.0, T;7, 24.1, D;12, 32.4). In T group 2 of 8 patients died due to severe vasospasm (6.9%). The complication in T group was epidural hematoma occurring in 2 patients. It was suggested that intraoperative injection of rt-PA with cisternal drainage may be most effective in reducing vasospasm among four methods and improving outcome of the patients with SAH.

119 CLINICAL EXPERIENCE OF RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR IN THE SUBARACHNOID HEMORRHAGE FOLLOWING THE ANEURYSMAL RUPTURE D.H. Han, C.K. Chung Department of Neurosurgery, Seoul National University College of Medicine, Seoul, Korea

Cerebral vasospasm is the most common cause of the morbidity and mortality in the subarachnoid hemorrhage (SAH) following the aneurysmal rupture. Recently there are several reports which insist that the fibrinolytic agents can ameliorate the development of vasospasm. Among them, the recombinant tissue-type plasminogen activator (rTPA) has the least frequent side effects. Authors report their clinical experience in which rTPA was used in 6 patients having the subarachnoid hemorrhage following the aneurysmal rupture.

The preoperative Hunt-Hess grade was II (3 patients) and III (3). The Fisher's SAH grade was II (1), III(2) and IV (3). The aneurysms were clipped within 4 days after rupture. After clipping, 10 mg of rTPA was administered into the subarachnoid space directly. In 4 patients whose preoperative computed tomography visualized the SAH, the SAH disappeared in 2 days (2 patients) or 7 days (2). Three patients had the clinical vasospasm. Among them one patients had the diffuse infarct. Systemic coagulopthay was not observed. Acute hepatic dysfunction occurred in one patient. However there were many intracranial hemorrhagic complications. One had the hemorrhagic infarct, 2 cerebellar hemorrhage, and 2 small epidural hematoma.

In authors' series, the SAH did not disappear in 24 hours. There was no evidence of increased systemic coagulopathy. However, there were many intracranial hemorrhagic complications. These results suggest that the dose-response relationship and the timing of application should be reconsidered.

120 EFFICACY STUDY OF INTRACISTERNAL RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (rt-PA) IN PATIENTS WITH SUBARACHNOID HEMORRHAGE. J.M. Findlay*, N.F. Kassell, W.M. Alves, G.L. Kongable, B.K. Weir, and the rt-PA Study Group. *Division of Neurosurgery, University of Alberta, 2D1.02 WMC, 8440-112 Street, Edmonton, Alberta, Canada T6G 2B7. A randomized, double blinded, placebo-controlled trial of intracisternal fibrinolytic therapy with recombinant tissue plasminogen activator (rt-PA) in patients with severe subarachnoid hemorrhage is being conducted in a number of North American Centers. Eligible are patients with thick subarachnoid clots on computed tomography (CT) undergoing surgery for aneurysm clipping within 72 hours of rupture. Treatment consists of a 10 ml intraoperative injection of either rt-PA (10 mg) or placebo into the opened basal cisterns adjacent to the completely repaired saccular aneurysm responsible for the hemorrhage. After allowing 15 minutes for drug circulation and absorption to subarachnoid clot the cisterns are irrigated with saline. Patients receive standard post-operative care, including nimodipine administration. A CT scan is obtained within 24 hours of surgery to assess for both cisternal clot clearance and new hemorrhage, and patients are followed clinically, with transcranial Doppler and cerebral angiography performed between the seventh and eleventh post-operative day. It has been estimated that 100 randomized patients (50 per group) will be required to determine if this treatment results in a significant reduction in severe, diffuse angiographic vasospasm and/or symptomatic vasospasm. Subarachnoid clearance, transcranial Doppler evidence of vasospasm, requirement of hypertensive, hypervolemic treatment and other therapy to reverse vasospasm, overall outcome and clinical safety will also be measured. At the time of abstract preparation the study is almost one-half complete and constant safety monitoring has not yet revealed any serious hemorrhagic complications probably attributable to treatment or any other medical event requiring interim analysis or cessation of the trial. An update on this study will be provided.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

121 QUANTITATIVE ANALYSIS OF THE THROMBOLYTIC EFFECT OF rt-PA, UROKINASE AND LYSL-PLASMINOGEN IN A CANINE MODEL OF SAH Y. Kajimoto, K. Yamada, S. Nagasawa, T. Ohta. Department of Neurosurgery, Osaka Medical College, Takatsuki, Japan

In intrathecal thrombolytic therapy, the optimum thrombolytic agents and their optimum doses have not been established. Thus, we measured and analysed the time course of the clot lysis for 24 hours in canine SAH model by intrathecal irrigation of different thrombolytic agents.

Subarachnoid clot was induced in adult mongrel dogs by infusion of autologous blood (10 ml) into the major cistern. Irrigation was performed between the major cistern and the spinal subarachnoid space with solutions of urokinase (UK) (24, 120, 600 or 3,000 IU/ml), rt-PA (500, 2,500 pr 12,500 IU/ml) and drug-free saline for 24 hours at a rate of 4 ml/hour. In some animals, irrigation with 10 ml of lysl-plasminogen (lys-plg) (90 CU/ml) for one hour preceded that with UK (120 IU/ml) for 24 hours. The rate of clot lysis was measured by the amount of hemoglobin in the drained fluid.

The clot lysis of UK or rt-PA increased in a dose-dependent manner up to 3,000 IU/ml (UK), or 12,500 IU/ml (rt-PA). Pretreatment with lys-plg markedly enhanced the thrombolytic effect of UK.

These results indicate that the clot lysis with intrathecal thrombolytic therapy can be increased by higher intrathecal concentration of rt-PA or UK, and by adding lys-plg prior to these drugs.

122 PREVENTION OF VASOSPASM BY VENTRICULO-CISTERNAL SELF-IRRIGATION USING UROKINASE AND SODIUM NITRITE S.Ikeda , N.Shida . Department of Neurosurgery, Kamitsuga General Hospital,Kanuma,Tochigi,Japan

Purpose: We investigated the effect of ventriculo-cisternal self-irrigation using urokinase(UK) and sodium nitrite(SN) on prevention of vasospasm, and measured sequential CSF levels of prostaglandins and lipid peroxides during this therapy to estimate preventing mechanism of SN. Subjects and methods: Consecutive 32 patients with SAH (Fisher's group 3) underwent early surgery and 19, 4 and 9 of these were in grade Ⅱ, grade Ⅲ and grade Ⅳ(Hunt and Kosnik grades),respectively. Postoperatively,3ml each of 100mM SN containing 6,000 international units of UK was intermittently infused to both of the ventricle and the cistern, and thereafter the drainage tubes were temporarily closed. This self-irrigation continued for 8 to 16 days with the outflow pressure of 15cm H_2O in ventricular drainage and 5cm H_2O in cisternal drainage. The comparison was made among following 3 groups : Group A(N=10)received the administration of UK and SN once daily. Group B(N=14)received twice daily. Group C(N=8)received twice daily accompanied by sodium ozagrel intravenously. The CSF samples were consecutively obtained from the ventricle at operation and from the cistern postoperatively. The CSF levels of prostaglandins and lipid peroxides were compared among group B,C and UK group(given UK only, reported in Nth International Conference on Cerebral Vasospasm,Tokyo,1990). Results: In group A,symptomatic vasospasm occurred in 3 patients who were in grade Ⅳ. However,2 of these easily recovered without any neurological deficit due to vasospasm. Anfortunately,remaining 1 died of hemorrhagic infarction. In group B, all cisternal clots usually vanished in a week, therefore symptomatic vasospasm didn't usually occur. Only 1 patient who was in grade Ⅱ died of symptomatic vasospasm resulted from postoperative thin subdural hematoma. However, angiographical vasospasm occurred in 4 patients with remaining clots in the insular cistern due to brain swelling. In contrast, there was no angiographical or symptomatic vasospasm in group C. Sequential angiograms after the administration of SN revealed vasodilatation at 1 hour, and then this effect continued for 4 hours corresponding to the increase of LCBF. On the other hand,the lipid peroxides concentrations in group B were significantly lower than those of UK group, and the 6-keto-$PGF_{1\alpha}$ concentrations in group B were significantly higher than those of UK group. The TxB_2 concentrations in group C were lower than those of group B and UK group. Conclusion: The present results demonstrated the ventriculo-cisternal irrigation therapy twice daily using UK and SN reduced the incidence of vasospasm. SN eliminates the vasospasmogenic activity by oxidizing oxyHb to metHb, and moreover induces vasodilatation and increase of LCBF. It is considered that these mechanism will suppress the production of lipid peroxides and increase that of PGI_2 in the arterial walls where organic changes were prevented by daily vasodilataion. The present study demonstrated irrigation therapy became more effective in the combination with thromboxane A_2 synthetase inhibitor such as sodium ozagrel.

123 THE COMBINATION THERAPY OF TISSUE PLASMINOGEN ACTIVATOR AND ANTI-THROMBIN III ON EXPERIMENTAL VASOSPASM M.Asada, J.Kong, M.Nakamura, K.Ehara, K.Fujita, N.Tamaki Department of Neurosurgery, Kobe University, Kobe, Japan

(Introduction) In the thrombolytic therapy by t-PA for acute myocardial infarction, thrombolysis generates increased thrombin levels and this reaction may cause the reocclusion in the coronary arteries. For preventing reocclusion, the efficacy of combination therapy of t-PA and anti-thrombin agent has been reported. Present studies were designed to investigate the preventive action of combination of t-PA and antithrombin III(AT-III) on the degrees of vasoconstriction following experimental SAH.

(Materials and Methods) A base line angiography was done in rabbits. Non-heparinized autologous arterial blood (2cc) was injected into the cisterna magna. Rabbits induced SAH were divided into 5 groups. Group 1 served as untreated animals. Group 2 recieved physiological saline cisternal injection(0.5ml) six hours after the induction of SAH.Group 3 recieved intrathecal injection of AT-III(25 units) in the same method. Group 4 recieved intrathecal injection of t-PA (10000 units) six hours after the induction of SAH. Group 5 recieved intrathecal injectionof AT-III(25 units) plus t-PA(10000 units) six hours after the induction of SAH. In each group, serial angiographies were done on day 1, day 3 and day 5. The diameters of the basilar arteries were measured.

(Results) The prominent vasoconstriction in the untreated group were observed on dayl and subsided on day 5. T-PA injection and AT-III injection group showed the statistically significant preventive action on day 1 and day 3. On the other hand, the combination group of t-PA and AT-III showed the same action on day 1, day 3 and day 5. Moreover, the combination group was statistically more effective than t-PA or AT-III group on day 3.

(Conclusion) The combined therapy of t-PA and AT-III was more effective to prevent vasospasm than the single t-PA or AT-III intrathecal injection.

124 STREPTOKINASE IN THE TREATMENT OF CEREBRAL VASOSPASM AFTER SUBARACHNOID HEMORRHAGE IN DOGS F.J. Espinosa, P.M. Gross, J.-H. Tao, K.O. Green, D.S. Wainman, J.J. Pang. Department of Surgery, Queen's University and Kingston General Hospital, Kingston, Ontario, Canada K7L 3N6

Intrathecal thrombolysis with use of t-PA and rt-PA after SAH has proved effective in preventing chronic vasospasm in monkeys. Also, within 24 hr after hemorrhage in cats streptokinase (SK) and streptodornase proved effective in lysing the SAH clots but produced diffuse meningoencephalitis. Streptokinase, however, has not been studied singly in chronic experiments to assess whether VSP may be prevented and the meningoencephalitis that develops when used with streptodornase does not occur. We studied 33 dogs of either sex under general anesthesia; they were randomly assigned to receive SK 150,000 U (1 ml) or saline (1 ml) intrathecally. Six animals died immediately after creation of the SAH and before they received SK or saline. Of the remaining 27 dogs available for analysis, 15 received SK and 12 saline 24 hr after the SAH via an Ommaya reservoir implanted at the time of the craniotomy. Variables measured or observed before and 7 days after SAH included neurological status, BP, vessel caliber on cerebral angiograms, structural and morphological changes of the cerebral arteries on electron microscopy, and the presence or absence of hematomas in the subarachnoid space and/or meningoencephalitis. In the placebo group delayed neurological deficit developed in 2 dogs 2 and 5 days after clot placement. In the SK group such deficit occurred in 1 dog 2 days after the SAH. Overall, vasospasm was more common and more severe in the SK group. Significant VSP (31% to 100% reduction in vessel calibre) developed in 25% (3/12) of the dogs in the placebo group, and in 66% (10/15) of the dogs in the SK group. The average percentage reductions in vessel calibre of the maximally constricted vessel in each dog was significantly different ($p = 0.04$) -- in the placebo, it was 23.4%, and in the SK group was 36.6%. Similarly the changes seen under electron microscopy were more severe in the SK group than in the saline group. No meningoencephalitic developed in any of the animals studied. SK at the dose used, did not prevent the development of vasospasm, and was ineffective in lysing the SAH clots. Saline reduced the incidence and severity of vasospasm, probably by diluting the concentration of vasogenic substances.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

125 **Prevention of Post-Operative Intracerebral Hemorrhage Using Topical Recombinant Factor XIII in the Rat** V. Laohaprasit, M.W. Edwards, M.R. Mayberg, *Department of Neurological Surgery, University of Washington, ZymoGenetics, Inc. Seattle, WA USA*

Intraoperative application of recombinant tissue plasminogen activator (tPA) is a promising new therapy for the prevention of cerebral vasospasm. Its use may be limited, however, by post-operative hemorrhage at the operative site and regions of injury from the initial hemorrhage. Factor XIII is an endogenous clotting factor which retards tPA-mediated thrombus degradation by cross-linking fibrin. To determine the efficacy of Factor XIII as a topical clot-stabilizing agent in preventing post-operative hemorrhage associated with coagulopathy, a rat model of experimental craniotomy and standardized bilateral frontal corticectomy was developed. In 25 rats (50 lesions), recombinant human Factor XIII or placebo solution were topically applied to corticectomy cavities after hemostasis was achieved; each animal served as its own control. In 20 rats, intraperitoneal heparin sulfate (100 units/kg/hour) was initiated 3 days after surgery and continually administered by Alzet pump for 7 days, compared to a control group of 5 rats receiving saline. The volume of intracranial hemorrhage was quantitatively determined from coronal sections using automated image analysis. Large (>50 mm^3) intracerebral hemorrhages were significantly more frequent in placebo (60%) compared to recombinant factor XIII (15%) treated lesions ($p<0.01$) in animals receiving heparin. Topical application of clot-stabilizing agents such as factor XIII may reduce the risk of post-operative intracranial hemorrhage associated with tPA.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

P1

TCD AND ICP VALUES IN THE ASSESSMENT OF THE TIME COURSE OF VASOSPASM FOLLOWING SUBARACHNOID HEMORRHAGE

A.L.Messina, P.Gaetani*, E.Benericetti and R.Rodriguez y Baena*
Department of Neurosurgery, Bormio and Sondalo Hospital and *Department of Surgery, Neurosurgery, IRCCS Policlinico S.Matteo, Pavia, Italy

Transcranial doppler (TCD) has been proposed as the technique of choice in detecting the course of arterial vasospasm following subarachnoid hemorrhage (SAH). Recent studies have pointed out that TCD recording is not always a reliable tool since in some cases a clear discrepancy between TCD values and neurological conditions indicating a symptomatic vasospasm is evident. In the present study we selected 52 patients admitted for SAH with the purpose to study the relationship existing between TCD values and data obtained with simultaneous recording of intracranial pressure (ICP). Mean flow velocities and resistance index (RI) were recorded every 12 hours after admission having a simultaneous recording of ICP through a subdural probe placed in the right temporal region regardless of the site of the aneurysm. We divided the patients to two subgroups, according to ICP measurements: group 1 (ICP < 20 mmHg) and group 2 (ICP > 20 mmHg). Clinical assessment was recorded according to the Hunt & Hess grading system. Mean velocity of middle cerebral artery was considered the most reliable and prognostic TCD parameter in the assessment of arterial vasospasm. Patients classified in group 1 had a RI lower than 0.5, while RI was higher than 0.6 in patients of group 2. In group 1 the highest flow velocity obtained by TCD was considered higher than normal values, with a mean value of 160 cm/sec ± 15); mean velocity in MCA territory was correlated to patients clinical conditions; in group 2 patients presented a higher clinical grade at admission, but the peaked MCA flow velocity was lower than normal values (mean : 87 ± 9 cm/sec), and was associated with a higher RI. Another important issue concerns the relationship between TCD values and CT classification of cisternal blood clots, as indirect index of intracranial pressure: there is a significant correlation between pulsatily index (PI) calculated in the MCA territory (which is directly related to the level of ICP) and CT classification only at day 1 after SAH (R = 0.577, t = 0.03), while the same relationship is not significant neither when mean values of arterial velocities are considered (R = 0.200; t = 0.494), nor when PI and CT data are compared 5 days after the hemorrhage. The results of the present study suggest that some TCD "false negative" measurements are correlated to a significantly high ICP condition and that the association of TCD and ICP monitoring may be of crucial interest in the management of patients suffering SAH.

P2

CALPAIN-CALPASTATIN SYSTEM OF CANAIN BASILAR ARTERY I. Yamaura, E. Tani, T.C. Saido, K. Suzuki, N. Minami, Y. Maeda Department of Neurosurgery, Hyogo College of Medicine, Hyogo; Tokyo Metropolitan Institute of Medical Science, Tokyo; and Institute of Applied Microbiology, University of Tokyo, Tokyo, Japan

Vasospasm was produced in the canine basilar artery by two-hemorrhage method, whereas tonic contraction was induced in the normal canine basilar artery by KCl or serotonin. Inactivated and activated forms of μ-calpain, and activity of calpastatin were examined in the basilar artery. In spastic group, μ-calpain was activated markedly on Day 0 and showed a continuous activation on Day 2 and Day 7, whereas μ-calpain was activated in the early contraction stage and thereafter inactivated in the later stage in the tonic groups. Calpastatin activity was significantly decreased in spastic group on Day 0, Day 2 and Day 7, whereas it was not significantly changed in the tonic groups. It would be suggested that the activity of μ-calpain resulting from the balance of μ-calpain and calpastatin in the basilar artery is enhanced continuously in the spastic group and transiently in the tonic groups, and that the continuous activation of μ-calpain in vasospasm probably induces proteolytic changes in the basilar artery.

P3

INACTIVITY OF PDGF-RECEPTORS IN CANINE BASILAR ARTERY K. Yamakawa, J.W. Peterson, R. Sibilia, M. Kaoutzanis, N.T. Zervas. Neurosurgical Service, Massachusetts General Hospital and Dept of Surgery, Harvard Medical School, Boston, MA

Activation of protein kinase C by increased levels of diacylglycerol (DAG) is an attractive candidate for mediator of prolonged constriction during cerebral vasospasm. We attempted to detect a relation between increased DAG content and sustained contraction in canine basilar artery using platelet-derived growth factor (PDGF), which is reported to increase DAG levels through activation of phospholipase C and promote vasoconstriction in some arterial preparations. In an in vitro chamber suitable for measurements of force development, DAG content in unstimulated segments of canine basilar artery in the apparatus (5.0±0.7 SEM pmol/μg protein, n=11) were not different from values measured in unmounted segments frozen shortly after excision (5.2±0.8, n=14). No significant changes in DAG content were found upon activation of prolonged near-maximal contraction with high potassium medium (4.6±0.7, n=5). Treatment with PDGF for 30 min at concentrations adequate to produce maximal reaction in rat aorta produced no contractile response in dog basilar artery and no significant change in DAG content (4.7±0.4, n=4). PDGF receptors are either absent or not coupled to phospholipase C activation in canine cerebral arteries.

P4

NEOMYCIN-INDUCED INHIBITION OF THE RESPONSE OF CEREBROVASCULAR SMOOTH MUSCLE CELLS AND CEREBRAL VESSELS TO OXYHAEMOGLOBIN B. Vollrath, B.K.A. Weir, D.A. Cook. Departments of Pharmacology and Surgery, University of Alberta, Edmonton, Alberta, T6G 2H7 CANADA

Because changes in intracellular levels of calcium (Ca_i^{2+}) are critical to the development of contractile force in smooth muscle, we have examined the effects of oxyhaemoglobin (O_2Hb) on the concentration of Ca_i^{2+} in cultured smooth muscle cells derived from primate cerebral arteries. There is a rapid increase in Ca_i^{2+} within 30 seconds of exposure to O_2Hb, and the concentration of Ca_i^{2+} continues to rise steadily, and after 24 hours is about three times the normal level. The initial rise in Ca_i^{2+} correlates well with changes in the intracellular level of inositol (1,4,5) trisphosphate ($Ins(1,4,5)P_3$) produced by the action of phospholipase C (PLC), and with the development of contractile force in isolated arterial rings. We have thus used the PLC inhibitor neomycin to investigate the mechanism of action of O_2Hb. Neomycin attenuates the early rise in intracellular calcium and inhibits the initial contractile response to oxyhaemoglobin in arterial rings. The sustained response to O_2Hb, and the later stages of the elevation of Ca_i^{2+} are also sensitive to neomycin, although the levels of $Ins(1,4,5)P_3$ return to control levels within a few minutes of exposure to O_2Hb. This implies either that there is a second, neomycin-sensitive mechanism which plays a role in the sustained contraction, or that the sustained response is critically dependent on elevation of $Ins(1,4,5)P_3$ which then triggers other processes.

POSTER SESSIONS

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

P5 FUNCTIONAL DAMAGE OF NITRIC OXIDE ACTIVITY AFTER SUBARACHNOID HEMORRHAGE IN DOGS Y.Kajita, T.Tanazawa H.Oyama, M.Takayasu, Y.Suzuki, M.Shibuya, K.Sugita. Department of Neurosurgery, Nagoya University, Nagoya, Japan

The synthesis and release of nitric oxide in vascular tissue is important to the maintenance of the basal tone of cerebral blood vessels. The effects of SAH on the function of nitric oxide in the basilar arteries of the two-hemorrhage model dogs were investigated by angiography. Intracisternal injection of L-arginine (10^{-5} ,10^{-4} mol), a substrate for the formation of nitric oxide, produced a long-lasting vasodilation in the basilar arteries of intact dogs, while N^G-monometyl-L-arginine (L-NMMA, 10^{-7}-$^{-5}$ mol), a NO synthesis inhibitor, reduced the basal diameter of the basilar arteries. Injection of L-arginine into the cisterna magna of the SAH dogs reversed the vasospasm on Day 4 and on Day 7, but vasidilatory duration induced by L-arginine in the spastic vessels was significantly shorter than that in intact vessels. L-NMMA showed no significant effects on vessel diameter in Day 4 and Day 7 dogs. Vasodilatory effects of L-arginine were enhanced by simultaneous injection of superoxide dismutase (SOD) which protect the degradation of nitric oxide. SOD also significantly increased the vasodilatory duration by L-arginine. These results suggest that nitric oxide contributes to the maintenance of the basal vascular tone,and that the vasodilatory function is severely damaged after SAH, while the ability to produce nitric oxide in vascular tissue is preserved.

P6 EFFECTS OF LP-805, A NOVEL VASODILATING AGENT, ON ION CHANNELS IN CULTURED ENDOTHELIAL CELLS. H. Zhang, M. Inazu, E.E. Daniel and B. Weir. Department of biomecial Sciences, McMaster University, Hamilton, Ontario and Neurosurgery, The universitry of Chicago, Chicago, Illinois.

Vasodilatation by LP-805, a newly synthesized vasodilator, is related to its opening of K channels and/or release of endothelium-derived nitric oxide in vascular smooth muscle. We investigated that the effects of LP-805 on membrane ion channels in cultured bovine pulmonary arterial endothelial cells and human umbilical vein endothelial cells. Under whole-cell patch-clamp, LP-805 (1 to 100 uM) increased outward K currents in a dose dependent manner. The increase of this K current was inhibited by TEA (1 mM) and 4-AP (5 mM), but not by glibenclamide (1-10 uM), and was partially recovered by wash. LP-805 decreased inward K current in a dose-dependent manner and this action was blocked by TEA (5 mM) and 4-AP (5 mM). LP-805 increased outward K current in human umbilical vein endothelial cells which was TEA sensitive. In cell-attached category, LP-805 (1 to 10 uM) activated an outward K conductance in a dose dependent manner. Changing pipette solusions from 140 mM KCl to either 120 mM CaCl2 or 140 mM NaCl (plus 5 mM CaCL2), LP-805 activates two inward conductances (30, 50 pS respectively). Those effects were reversed by washout. These results indicate that LP-805 increases calcium influx into endothelial cells through nonspecific cation channels, which may activate calcium dependent K channel and produce a positive feedback to the influx of calcium, and release of nitric oxide in cultured endothelial cells. The possible direct effects of LP-805 on K channels can not be excluded.

P7 CHANGES OF CEREBROVASCULAR RESPONSES TO NITROGLYCERIN AFTER SAH T. Takase , T. Ohta , R. Ogawa, M. Tsuji, Y. Tamura , Y. Yoshizaki , S. Kazuki, K. Yamada,
Department of Neurosurgery, Osaka Medical College , Osaka, JAPAN

INTRODUCTION : Nitroglycerin (GTN) is a vasodilator and acts as an extrinsic EDRF after converted to nitric oxide (NO) in smooth muscle cells. We investigated the cerebrovascular responses to GTN applied either intra-(IL) or extraluminally (EL) using a perfusion system. We also investigated inhibitory effects of extraluminal oxyhemoglobin (oxyHb) and subarachnoid hemorrhage (SAH) on GTN.

METHODS: Japanese white rabbits were anesthetized and exanguinated. The basilar artery was removed as a cylindrical preparation and perfused at a constant flow rate. Changes in the tone of the artery were detected as changes in the perfusion pressure. 1) After submaximal tone was induced with 40mM KCl applied bilaterally or 10^{-8} M of endothelin (ET) applied IL, 10^{-7}M-3× 10^{-5}M of GTN was applied IL or EL in a cumulative manner. 2) Following ten minutes of pretreatment with 10^{-6} M extraluminal oxyHb, effects of GTN were studied in the same manner. 3) RABBIT SAH MODEL; Unheparinized autologus blood (1ml/kg) was injected into the prepontine cistern. Two days after SAH, the rabbit was sacrificed and the basilar artery was removed and connected to the perfusion system.

RESULTS: 1) GTN caused dose-dependent relaxation. IL application of GTN had greater relaxing effect than EL application but it was not significant. 2) Extraluminal oxyHb significantly inhibited the relaxing effect of GTN applied both IL and EL. 3) Relaxing effect of GTN was not attenuated on the artery from SAH model when precontraction was made by KCl. On the artery precontracted by ET, however, the effect of GTN was significantly diminished.

CONCLUSION: 1) Extraluminal oxyHb may inhibit vasodilatory effect of intracellular NO. 2) SAH may change the sensitivity of smooth muscle cells to NO. These may contribute to the pathogenesis of cerebral vasospasm.

P8 IMMUNOHISTOCHEMICAL IDENTIFICATION OF NON-MUSCLE COMPONENTS IN HUMAN CEREBRAL VASOSPASM Y. Terai, R.R. Smith, D.H. Bernanke*, K. Iwasa. Departments of Neurosurgery and Anatomy*, University of Mississippi Medical Center, Jackson, MS

Myofibroblasts were identified originally in granulation tissue and assumed to exert contractile force by extracellular collagen remodeling. Cells cultured in our laboratory from five cases of human cerebral arteries with vasospasm after subarachnoid hemorrhage showed ultrastructural characteristics of myofibroblasts. We examined cytoskeletal and extracellular matrix proteins of myofibroblasts from cultures and in situ preparations by means of indirect immunofluorescence. Cultured myofibroblasts were consistently positive for vimentin and non-muscle myosin. However, α-smooth muscle actin and desmin, markers of smooth muscle differentiation, were expressed in only a few cells per culture. In samples of human cerebral arteries with vasospasm, several types of collagen were identified by immunohistochemistry in the subintimal area in which myofibroblasts were found. Taken together, these observations suggest that proliferating myofibroblasts in human cerebral arteries after subarachnoid hemorrhage are not smooth muscle cells and that non-muscle components play important roles in human cerebral vasospasm.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

P9 IMMUNOBLOTTING OF CONTRACTILE AND CYTOSKELETAL PROTEINS OF CANINE BASILAR ARTERY IN VASOSPASM N. Minami, E. Tani, Y. Maeda, I. Yamaura, M. Fukami Department of Neurosurgery, Hyogo College of Medicine, Hyogo, Japan

Vasospasm was produced in the canine basilar arteries by a two hemorrhage method, whereas tonic contraction was produced in the normal canine basilar arteries by a local application of KCl or serotonin after transclival exposure. The contractile and cytoskeletal proteins in the spastic and tonic basilar arteries were studied by immunoblotting. In spastic group on Day 2, actin, myosin, desmin and filamin were degradaded partially whereas talin and α-actinin moderately. Vinculin remained intact. In spastic group on Day 7, actin and desmin were decomposed partially, filamin moderately, myosin and vinculin substantially, and talin, vinculin and α-actinin almost completely. In KCl and serotonin group, myosin, filamin, talin and α-actinin were degradaded partially and actin, desmin, vinculin were not degraded. It would be suggested that the degradation of intraceller devices responsible for contraction of basilar artery is generally more severe in spastic group than in KCl or serotonin group and progressive with the passage of time after subarachnoid hemorrhage in vasospasm.

P10 Effect of nicorandil on chronic vasospasm. T. Matsui, (*)T. Nagafuji, (*)T. Miyauchi, (*) T. Koide, T. Asano. Department of Neurosurgery, Saitama Medical Center/School, Saitama, Japan. (*) Exp. Res. Lab V. Chugai Parmaceut., Co. Ltd., Shizuoka, Japan.

The present study aimed at examining therapeutical effect of nicorandil on chronic vasospasm, using beagle dogs subjected to "two hemorrhage" and its dilatory effect on the phorbol-12,13-diacetate [PDA]-induced contraction of the canine basilar artery. <1> A total of 12 animals, weighing 7 to 12 kg and either sex, were randomly assigned into saline control and nicorandil-treated groups. Immediately after the second induction of SAH, animals started to receive the agent via the venous route at the constant rate of 10 μg/kg/ minute for six hours. On Days 4, 5 and 6, the agent was given twice at the same rate for three hours. Prior to the first and final angiographies, blood flow of the vertebral artery (VBF) was measured with electro-magnetic flowmeter. After the final angiography, animals were terminated by exanguination. The basilar artery was excised for measuring cGMP.<2> Using ring-segments of the canine basilar artery at the resting tension of 3 g, isometeric tension was recorded to examine effect of nicorandil on PDA-induced contraction. Nicorandil significantly ameriolated both angiographic narrowing and decrease in VBF following SAH together with dose-dependent inhibition of PDA-induced contraction. However, there was no significant difference in cGMP content of basilar artery between the both groups. The present data indicate that nicorandil provides a useful way of treatment of chronic vasospasm.

P11 EFFECT OF SINGLE INTRAVENTRICULAR BOLUS INJECTION OF t-PA ON EXPERIMENTAL VASOSPASM T. Nakagomi, K. Yamakawa*, T. Sasaki*, A. Tamura, and I. Saito + Department of Neurosurgery, Teikyo University, *University of Tokyo, +Kyorin University, Tokyo, Japan

The purpose of this study was to examine the effect of single intraventricular bolus injection of tissue plasminogen activator (t-PA) on experimental cerebral vasospasm. The canine "single hemorrhage model" was used. One ml of t-PA (250 μg) was injected through the needle inserted into the left lateral ventricle 3 hours following the subarachnoid blood administration (Day 0). To evaluate the magnitude of vasospasm, the diameter ratio was calculated as the percent of the basilar artery diameter of a given angiogram to that of its control. The degree of residual subarachnoid clot was also examined. In the non-treated group, the diameter ratio of the basilar artery on Day 3 was 59.8±3.0 (mean±SEM) % (n=6). On the other hand, in the t-PA-treated group, diameter ratio was 83.7±2.9 % (n=6). The difference in the diameter ratio between two groups was statistically significant ($p<0.01$). Remarkable subarachnoid clot around the basilar artery was still noted in the non-treated group. In the t-PA-treated group, however, marked lysis of subarachnoid clot was observed. Hemorrhagic complications (one intracerebral hematoma and two subcutaneous hematoma) have occurred. These results indicate that an intraventricular bolus injection of t-PA is effective in disolving the subarachnoid clot and preventing vasospasm as well as an intracisternal injeciton of t-PA.

P12 MECHANISM OF VASODILATATION BY APPLICATION OF PULSED-DYE LASER IN VITRO. M. Kaoutzanis, J.W. Peterson, R. Anderson, D.J. McAuliffe, R. Sibilia, M. Yokota, N.T. Zervas. Neurosurgical Service and Wellman Laboratories of Photomedicine, Massachusetts Gen. Hospital, Boston, MA

In an attempt to clarify the mechanisms which underlie pulsed-dye laser induced vasodilatation, rabbit carotid arteries were mounted in vitro in a double-cannulation, pressure-perfusion apparatus and constricted by extraluminal application of high-K+ solution. As reported earlier, intraluminal laser pulses at 575 nm wavelength dilated the vessels when the luminal perfusate contained intact or lysed erythrocytes. Pulsed-dye laser vasodilatation does not necessarily require the presence of hemoglobin however. The same phenomenon was obtained with statistically better results using an inert dye such as Evans' blue when the laser light wavelength was tuned to values well within the Evans' blue absorption spectrum (480 nm). In both studies (hemolysate and Evans' blue), the optical density of the perfusate directly influenced the vasodilatory response. Percentage dilatation increased relative to OD, the number of applied pulses and the total applied energy. Results were the same for normal vessels and vessels denuded of endothelium. Based on these results, we believe that pulsed-dye laser induced vasodilatation is a purely physical process resulting from the optical absorption of laser energy by the intraluminal medium and its direct transmission to the vessel wall.

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

NOTES

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

NOTES

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press

NOTES

https://doi.org/10.1017/S0317167100048423 Published online by Cambridge University Press