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Stroke with Subarachnoid Hemorrhage: Assessment of Cerebrovascular Pressure Regulation and Simulated Cerebrovascular Resistance

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SUMMARY

Monitoring methods designed to assess cerebrovascular regulation and increased cerebrovascular resistance (CVR) of patients with subarachnoid hemorrhage (SAH) would facilitate therapeutic intervention and potentially reduce secondary complications. The aim of this study was to assess changes of cerebrovascular regulation and CVR by evaluating changes of cerebrovascular pressure transmission in patients with SAH.

Admission Hunt-Hess grades, Fisher scores, Glasgow Outcome Scores (GOS) at 6 months, and pressure recordings were obtained from 20 patients. Biomechanical models of cerebrovascular pressure transmission were constructed over one-minute intervals for the initial and final two hours of post-hemorrhage monitoring.

Classified according to the GOS score at 6 months, eight patients died (GOS 1), five were severely disabled (GOS 3), and seven patients were moderately disabled (GOS 4). During the initial monitoring period 100%, 80%, and 28.6% of groups with GOS 1, 3, and 4 demonstrated impairment of cerebrovascular regulation; whereas, in the final monitoring period 100%, 100%, and 14.3% respectively demonstrated impairment. Between monitoring periods, simulated CVR (sCVR) significantly increased ($p < 0.001$) for patients with GOS 1 and 3 and decreased for those with GOS 4 with mean resistance for the latter group significantly lower ($p > 0.001$) than other means.

Loss of cerebrovascular regulation and increased sCVR were observed in SAH patients with poor outcome.

Keywords

subarachnoid hemorrhage; cerebrovascular pressure transmission; cerebrovascular pressure regulation; cerebrovascular resistance

INTRODUCTION

Studies of patients with subarachnoid hemorrhage indicate that cerebral hemodynamics are commonly disturbed in the acute stage [6,7,9]. CBF may be reduced in patients without vasospasm [6,9], and parenchymal arterial vessels demonstrate an impaired autoregulatory response [12]. Previously we have shown that changes in the highest modal frequency (HMF) of cerebrovascular transmission, the dynamic relationship between arterial blood pressure (ABP) and intracranial pressure (ICP), relative to changes of cerebral perfusion pressure (CPP) are a means to assess cerebrovascular regulation [3–4]. More recently we have developed a two-step modeling technique by incorporating the derived modal frequencies of the numerical model and the actual blood pressure recording with a physiologically-based biomechanical model to produce a simulated ICP recording which matches the actual ICP recording. Using this modeling procedure we have validated that laboratory measures of changes of arteriolar resistance and compliance during induced hypercapnia are replicated by the physiologically-based biomechanical model [5]. The aim of this retrospective study was to assess changes of cerebrovascular regulation and cerebrovascular resistance by evaluating changes of cerebrovascular pressure transmission in patients with SAH using the two-step modeling method.

MATERIALS AND METHODS

Standard ICP and ABP monitoring is part of the management strategy of adult stroke patients with SAH at The National Hospital, Oslo, Norway with the aim of controlling ICP. The attributes of the patients grouped according to the Glasgow Outcome Score (GOS) at 6 months and the admission Hunt-Hess (HH) grades and Fisher scores (FS), age, and sex are given in Table 1. Pressure recordings were labeled such that the patients could not be identified by the Memphis group. The Institutional Review Board at The University of Memphis approved the data analysis protocol.

Pressure recordings were digitized at 100 Hz. Recording periods were not uniform; mean monitoring time ($\pm$ S.D.) was 33.6 ($\pm$ 30.4) hrs. Some patients were monitored periodically over a course of several days while others were only monitored once. Mean values of HMF and simulated CVR (sCVR) were determined for the first two hours, middle two hours, and last two hours of each monitoring period.

The first step of the two step modeling method uses system identification modeling; the details of which have been previously reported (3–5). Briefly, system identification modeling method produces a black box model with a simulated output that matches the actual output by minimization of the least squares difference between the actual and simulated digitized output files (8). Of critical importance in the use of system identification modeling is the selection of the generalized description of the dynamic process to be modeled (8). We chose the physiologically-based biomechanical model proposed by Czosynka and his colleagues (2) to provide the basis of the required generalized dynamic differential equation of cerebrovascular pressure transmission. The autoregressive moving average system identification technique is applied to each 6000 paired samples of digitized pressure recordings of 1 min to obtain the modal frequencies of cerebrovascular pressure transmission. For the brief period on which each

numerical model is based, perturbations of ABP and ICP are assumed to be small and cerebrovascular pressure transmission is considered to be linear and time-invariant.

In the second step of the modeling method, the mean ($\pm$ S.D.) values of the modal frequencies derived by the first step numerical model and the corresponding 1 min interval of ABP recording are used to guide the manipulation of the parameters of the physiologically-based biomechanical model such that the simulated 1 min recording of ICP matches the actual ICP recording over the interval. Of note is that three modifications of the biomechanical model proposed by Czosynka and colleagues (2) were implemented. First, the description of the resistance of the arterial-arterioles and capillaries was slightly modified by placing the element representing the arterial-arteriolar bed at the mid-point, as it has been modeled by others previously (1). Secondly, in addition to the representation of the bridging veins with variable resistance, cerebral veins within the parenchyma were also considered to vary. Thirdly, the representation of venous sinus pressure was replaced by an external venous resistance component and connected to a central venous pressure generator as previously modeled (11). A MATLAB algorithm was constructed to simulate ICP for each ABP recording and the corresponding numerically derived modal frequencies for each modeling interval. The algorithm was designed to manipulate the resistance and compliance elements of the physiologically-based biomechanical model such that the minimum square error for the 6000 sample interval between: 1) the actual and simulated ICP recordings; 2) the numerical model value of HMF and the biomechanical value of HMF; and 3) the numerical model value of dampening factor (DF) of the lower modal frequencies and the DF of the biomechanical model were minimized. Use of DF to represent the dominant two modal frequencies simplified the computation of matching the numerically derived and simulated lower modal frequencies by eliminating the need for complex arithmetic for the condition of an under-damped system. Values of each element of the biomechanical model were manipulated. Initially a normal CBF was assumed to be 600ml/min (10–11) which corresponds to a CBF value of 40 ml/100 gm/min for an assumed brain weight of 1.5 kg. Both compliance and resistance elements were allowed to range over values consistent with those reported in previously published modeling studies of intracranial pressure dynamics (2,11). Compliance of the arterial/arteriolar bed was allowed to range from 0.01 to 10 ml/mmHg while venous and intracranial compliance were varied between 0.01 to 2 ml/mmHg (2,11). Venous resistance varied from 0.025 to 0.5 mmHg-100gm-min/ml and resistance of the arterial-arteriolar bed varied from 0.5 to 6.25 mmHg-100gm-min/ml (11). A maximum mean squared error of 0.6 and the minimum correlation value of 0.9 between both actual and simulated ICP recording was used to initialize the square error values. The parameters of the biomechanical model were estimated by a recursive algorithm to obtain a best fit set which produced a minimum least square error and maximum correlation value for each segment of the pressure recording. Because simulated arterial-arteriolar capillary resistance was much greater than simulated cerebral venous resistance, we used the value of arterial-arteriolar capillary resistance to provide an assessment of simulated cerebrovascular resistance (sCVR).

All mean values are reported $\pm$ standard deviation. In all cases, the degree of significance between two mean values was determined by using the paired t-test. The correlation between highest modal frequency (HMF) and CPP was used to assess cerebrovascular regulation for the initial and final two-hours of monitoring (3,4). An inverse relationship between HMF and CPP is an indication of intact regulation; whereas, a direct relationship indicates impaired regulation. For each GOS-group the percentage of patients with impaired regulation during the initial two hours and final two hours was computed.

RESULTS

Mean values of HMF and sCVR at the beginning, middle, and final hour of each monitoring session are plotted (see Fig. 1). GOS 1 and GOS 3 groups demonstrated trends of a decrease in HMF and an increase of sCVR with time; whereas, patients in the GOS 4 group demonstrated opposite trends. Grand mean regression line slopes ($\pm$ SD) of HMF/day and sCVR/day for GOS 4 patients were 2.95 ($\pm$ 0.56) Hz/day and -0.45 ($\pm$ 0.07) mmHg-100 gm-min/ml/day and significantly ($p < 0.001$) different compared to the corresponding mean values of both GOS 1 and GOS 3 groups at -0.58 ($\pm$ 0.17) Hz/day and 0.39 ($\pm$ 0.16) mmHg-100 gm-min/ml/day and -2.23 Hz/day and 0.41 ($\pm$ 0.06) mmHg-100 gm-min/ml/day, respectively. The relationship between HMF and CPP was used to assess cerebrovascular regulation [3,5]. An inverse relationship between HMF and CPP is an indication of intact regulation; whereas, a direct relationship indicates impaired regulation [3,5]. Mean values of initial two hours and final two hours monitored post hemorrhage, CPP, sCVR, and the percentage of the number of patients within each GOS group determined to have impaired regulation for the initial two hours and final two hours of monitoring post hemorrhage were computed (see Table 2). During the initial two hours of monitoring 100%, 80%, and 28.6% of patients with 6-month GOS of 1, 3, and 4 respectively demonstrated impaired regulation; whereas, in the final hours 100%, 100%, and 14.3% respectively demonstrated impairment. Between the initial two hours and final two hours of monitoring, sCVR significantly increased ($p < 0.001$) for patient with GOS 1 and 3 and decreased for those with GOS 4. The mean value of sCVR during the final monitoring hour was significantly lower ($p < 0.001$) for patients with GOS 4. This value reflected a simulated CBF of 26.4 ml/100 gm-min; whereas the corresponding mean values of sCVR for the GOS 1 and GOS 3 groups reflected ischemic simulated CBF values of 9.9 and 9.5 ml/100 gm-min respectively.

DISCUSSION

The new findings of this retrospective study are that loss of cerebrovascular regulation occurs early following SAH and model-derived cerebrovascular resistance progressively increases for patients with poor outcome after SAH. In contrast, intact cerebrovascular regulation with a progressive decrease of model-derived cerebrovascular resistance was observed in those with more favorable outcome. These findings are also consistent with an earlier study that found assessment of loss of cerebrovascular pressure regulation within 1–6 days post-hemorrhage is predictive of poor outcome (7).

Caution should be made when relating these data to outcome since the numbers of patients in each group were low and only two two-hour periods, the first two hours and final two hours of monitoring, were used to evaluate cerebrovascular pressure regulation. Neither angiographic images nor evaluations for symptomatic vasospasm nor measurement of CBF were available. Delayed vasospasm of conducting vessels may have contributed to the loss of cerebrovascular regulation. However, because of the early loss of cerebrovascular regulation and significant increase of the model derived resistance sCVR it is likely that increasing more generalized vasoconstriction of the microvasculature is involved.

In conclusion, in the early stages of Aneurysmal SAH loss, of cerebrovascular regulation and increasing values of model-derived cerebrovascular resistance were observed in patients with poor outcome.

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Figure 1. Trends in HMF and sCVR for GOS 1, 3, and 4 Patients vs. Days from Occurrence of Subarachnoid Hemorrhage

Each symbol represents a mean value of 120 one-minute values plotted with standard error bars within each symbol. Thin solid line connects values at the initial, middle, and final two hour intervals of each contiguous monitoring period. Top. GOS 1: As HMF decreased ($p < 0.001$) with time sCVR increased ($p < 0.05$). Middle. GOS 3: As HMF decreased ($p < 0.001$) with time sCVR increased ($p < 0.025$). Bottom. GOS 4: As HMF increased ($p < 0.001$) with time sCVR decreased ($p < 0.01$). Dashed line through each graph represents regression line of all values.

Table 1
Attributes of Patients Grouped According to GOS: Sex, Age, and Fisher Score and Hunt-Hess Grade

GOS	N	Sex (F(M))	Age(+/-SD) yrs	FS ¹ (+/-SD)	HH ² (+/-SD)
1	8	5(3)	51.6(10.8)	3.2(0.3)	4.5(1.1)
3	5	2(3)	61.8(10.4)	3.4(0.2)	3.4(1.1)
4	7	4(3)	53.4 7.1	2.6(0.6) ¹	3.6(1.4)

¹ Assumes continuous scale of category driven integer scales

² Level of significance between mean of GOS 4 and means of GOS 1 and 3 is p < 0.025

Table 2
Mean(± S.D) of Initial and Final Monitoring Time Post Hemorrhage, CPP, sCVR and Percent Impaired Regulation at each Monitoring Period

GOS	N	Initial Time (+/-SD)	CPP (+/-SD)	Percent Impaired Reg.	sCVR (+/-SD)	Final Time (+/-SD)	CPP (+/-SD)	Percent Impaired Reg.	sCVR (+/-SD)
		day	mmHg		mmHg-min- 100g/ml	day	mmHg		mmHg-min- 100g/ml
1	8	1.7(0.8) ^{1,2}	74.8(9.7)	100 8/8	4.3 (2.2) ³	3.8(1.5)	68.1(9.0)	100(8/8)	6.9 (0.8) ³
3	5	3.6(1.5) ¹	72.3(9.8)	80.0(4/5)	3.0(0.20) ⁴	4.8(1.3)	69.5(10.8)	100(5/5)	7.3 (0.9) ⁴
4	7	3.0(1.4) ²	77.4(8.3)	28.6(2/7)	3.9(1.5)	3.6(1.4)	79.1(8.0)	14.3(1/7)	3.0 (1.6) ⁵

¹, ² Significant difference of GOS 1 initial time from GOS 3 (p < 0.01)¹ and GOS 4 (p < 0.05)²
³ Significant difference between initial and final mean values of SCVR for GOS 1 (p < 0.01)
⁴ Significant difference between initial and final mean values of SCVR for GOS 3 (p < 0.001)
⁵ Significant difference of mean SCVR GOS 4 from means of GOS 1 and 3 at p < 0.001