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Assessment of Cerebrovascular Resistance with a Model of Cerebrovascular Pressure Transmission

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Abstract

A method to assess continuous changes of cerebrovascular resistance based on a biomechanical model of cerebrovascular pressure transmission is developed. Such a method provides an end-point measure to assess new and/or existing management strategies during intensive-care management of patients with brain injury. Changes of both pial arteriolar resistance and cerebrovascular resistance derived by a physiologically-based biomechanical model of cerebrovascular pressure transmission, the dynamic relationship between arterial blood pressure (ABP) and intracranial pressure (ICP), were compared to test the validity of the modeling procedure. Pressor challenge was administered to normoxic (N=5) and hypoxic (N=5) piglets equipped with closed cranial windows. Pial arteriolar diameters were used to compute arteriolar resistance. Percent change of pial arteriolar resistance (ΔPAR) and percent change of model-derived cerebrovascular resistance (ΔsCVR) in response to pressor challenge were computed. During intact cerebrovascular regulation and during hypoxia induced impairment of cerebrovascular regulation, changes in pial arteriolar resistance were accurately predicted by the proposed modeling method designed to assess changes of cerebrovascular resistance.

Keywords

cerebrovascular pressure transmission; cerebrovascular resistance and pressure regulation

INTRODUCTION

Cerebrovascular resistance has been reported to change following brain injury. Patients with stroke and subarachnoid hemorrhage may demonstrate progressive cerebrovascular constriction and vasospasm [1]; while traumatic brain injury has been associated with hypoxia [2], a potent vasodilator [3]. A method to assess continuous changes of cerebrovascular resistance may be a useful adjunctive means to assess new and/or existing intensive care management strategies. Previously we have developed a modeling procedure of cerebrovascular pressure transmission, the dynamic relationship between arterial and intracranial pressure, which replicates changes of cerebrovascular resistance and compliance during induction of acute hypercapnia [4]. The present laboratory study was designed to examine changes of cerebrovascular resistance to pressor challenge during normoxia and hypoxia. Both changes of pial arteriolar resistance and cerebrovascular resistance derived by the modeling procedure of cerebrovascular pressure transmission were examined. Arterial

blood pressure and intracranial pressure were simultaneously monitored in piglets equipped with cranial windows. Computation of pial arteriolar resistance as an index of vascular regulatory responses was determined from measurement of pial arterial diameter. The aim of the study was to test the hypothesis that changes in model-derived cerebrovascular resistance derived by the biomechanical modeling procedure accurately predicts corresponding changes of pial arteriolar resistance to pressor challenge during normoxia and during hypoxia.

METHOD AND MATERIALS

Laboratory Preparations

Using a protocol approved by the Animal Care and Use Committees of The University of Memphis and The University of Tennessee Health Science Center, α -chloralose anesthetized piglets ranging in weight from 2 to 4 kg were studied. In each piglet a cranial window was placed and video micrometer recordings of pial arteriolar diameter were made as described previously (6). Arterial blood gases were periodically assessed with an Instrumentation Laboratory Gem Premier 3000 blood analyzer. The tone of the cerebral vasculature was manipulated by reducing the fraction of O₂ delivered by the ventilator so that mild hypoxia was induced. During both normoxia and hypoxia, pressor challenge was administered by intravenous administration of vasopressin at 0.4 ug/kg/min for 5 min.

Pressure Recording and Averaging Technique

ICP recordings were obtained with an intraparenchymally inserted fiberoptic transducer (Camino Direct Pressure Monitor, Camino Laboratories, San Diego, CA). Recordings of ABP were obtained via a fluid filled cannula in the femoral artery with a SpaceLabs Model 90623A Monitor, Redmond, WA. The bandwidth of ABP channel of this monitor is 40 Hz with a $\pm 15\%$ variation. Each recording was digitized at a rate of 250 samples/s with a system previously described. For each preparation, mean values of ABP, ICP, and cerebral perfusion pressure (CPP), the difference between ABP and ICP, were determined for each 8 s interval and six consecutive intervals were used to compute the means for the baseline and pressor challenge conditions.

Pial Arteriolar Diameter Measurement and Resistance Calculation

A videomicrometer with magnification of 3600X was used to video tape the diameter of three arterioles during the experiment. The video recording was then converted to still- image frames using OSS Video Decompiler software One Stop Soft Inc, www.onestopsoft.com, at a rate of 30 frames per second. A tracking algorithm was implemented using MATLAB software to measure the diameter of arterioles during the experiment. Each frame was converted to gray scale and contrast adjusted to enhance the arterioles from the background. A region of interest on the arteriole was then chosen for diameter measurement. A threshold intensity value was set to distinguish between background and the arteriole within the chosen region. The diameter was then computed based on the number of pixels whose intensity values were lower than the selected threshold value iteratively for every frame. The mean value of pial arteriolar diameter (PAD) was computed on at least 7200 frames during a period of continuous steady-state conditions. Across all piglets the range of arteriolar diameter used in the computation of resistance was between 30 μ m and 70 μ m.

Computation of Pial Arteriolar Resistance and Percent Change Arteriolar Resistance

Based on the biomechanics of steady-state laminar flow in a cylindrical tube (5), the resistance of a pial arteriole can be estimated as:

$$R=128 \times \text{blood viscosity}/(\pi \times \text{PAD}^4) \quad (1)$$

With the use of this equation pial arteriolar resistance (PAR) based on a 1 mm length was computed on the assumption that the coefficient of viscosity for whole blood was 0.0027 N-s/m² at 37 C°. Also, percent change of arteriolar resistance (%ΔPAR) was calculated as:

$$\% \Delta \text{PAR} = [(\text{PAD}_{\text{baseline}}/\text{PAD}_{\text{challenge}})^4 - 1] \times 100 \quad (2)$$

A Two Step Modeling Method of Cerebrovascular Pressure Transmission

In the first step of the two step modeling method uses system identification modeling the details of which have been previously reported (6-7). 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). The physiologically-based biomechanical model proposed by Czosynka and his colleagues (9) is used 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 2000 paired samples of digitized pressure recordings of 8 s 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. This strictly numerical black box model enables the computation of the modal frequencies of the cerebrovascular pressure transmission which are the roots of the polynomial equation:

$$\lambda^3 + aa_2 \lambda^2 + aa_1 \lambda + aa_0 = 0 \quad (3)$$

The highest modal radian frequency (HMF) is defined as the eigenvalue with the greatest absolute value and is converted to modal frequency by division by 2*π. The other two eigenvalues are the dominant modes. The dampening factor (DF) of the process defines whether dominant modes result in a process that is over-damped or under-damped. If the two eigenvalues are real then the process is overdamped and DF is greater than one; where as, if the eigenvalues are complex conjugates then the process is underdamped and DF is less than one. As DF of a process approaches zero, the process demonstrates more resonant characteristics.

In the second step of the modeling method the mean values of the modal frequencies derived by the first step numerical model and the corresponding 8 s interval of ABP recording are used to guide the manipulation of the parameters of the physiologically-based biomechanical model such that the simulated 8 s recording of ICP matches the actual ICP recording over the interval. Of note is that three modifications of the biomedical proposed by Czosynka his colleagues (9) were implemented. First, the description of the resistance of the arterial-arteriolar bed was slightly modified by placing the element representing the arterial-arteriolar bed at the mid-point as it has been modeled by others previously (10). 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 sinus pressure was replaced by an external venous resistance component and connected to a central venous

pressure generator as previously modeled by others (11-13). Specifically, MATLAB software (The MathWorks Inc., Natick, MA) was used to simulate the biomechanical model using a modified state space description of the biomechanical model previously reported (13). The MATLAB model computation was constructed to simulate ICP for each ABP recording and the corresponding numerically derived modal frequencies for each modeling interval. During the computation the resistance and compliance elements of the biomechanical model were manipulated such that the minimum square error for the 2000 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 an under-damped system condition. Values of each element of the biomechanical model were manipulated. Both compliance and resistance elements were allowed to range over values consistent with those reported in previously published modeling studies of intracranial pressure dynamics (9,11-14). Compliance of the arterial/arteriolar bed was allowed to range from .01 to 10 ml/mmHg while venous and intracranial compliance were varied between 0.01 to 2 ml/mmHg (9,11,12,14). Venous resistance varied from 0.1 to 2 mmHg/ml/s and resistance of the arterial-arteriolar bed varied from 2 to 25 mmHg/ml/s (11, 12,14). 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 the model computation 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 ten times that of the model-derived cerebral venous resistance, the value of the resistance parameter representing both arterial-arteriolar resistance and capillary resistance was used to provide an assessment of model-derived cerebrovascular resistance (sCVR).

Statistical Methods

All mean values are reported with $\pm$ standard error of the mean. In all cases, the degree of significance between two mean values was determined by using the t-statistic.

RESULTS

A summary of the group mean values of ABP, ICP, and CPP for the baseline and challenge conditions for the normoxic control group and the hypoxic treated group is given in Table I. Also presented are the grand mean values of the arterial blood gas parameters of pH and partial pressure of CO₂ (pCO₂) and oxygen (pO₂) at baseline for each group. No differences in either pH or pCO₂ were observed. However, the mean value of pO₂ was in the hypoxic range and significantly lower than that determined for the normoxic control group. For both groups pressor challenge increased ABP and CPP increased. However, mean ICP decreased for the control group and increased for the hypoxic group (see Table 1).

Group mean values of PAD, PAR, and sCVR for the baseline and challenge conditions are given in Table 2. The orders of magnitude difference between PAR and sCVR represents the difference between the high resistance of arteriole and that of the global resistance of the arterial-arteriolar bed and capillaries with a large cross sectional area. To compare changes in microvascular resistance to the global estimates of changes of cerebrovascular resistance derived by the modeling method percent change of PAR and sCVR were plotted against percent change of CPP (see Figure 1). Consistent with intact pressure regulation of cerebral blood flow (CBF), the normoxic control group demonstrated constriction and an increase of both PAR

and sCVR as CPP increased; whereas, the hypoxic group demonstrated impaired regulation by dilation and a decrease of both PAR and sCVR as CPP increased.

DISCUSSION

The new finding of this study is that changes in pial arteriolar resistance are accurately predicted by equivalent changes of model-derived cerebrovascular resistance derived by a physiologically-based biomechanical modeling procedure. Pressor challenge during the control normoxia condition and during hypoxia resulted in similar percent changes of the values of both resistances, even though there is a difference of several orders of magnitude in the values of resistance between the computed values of PAR and sCVR. During normoxia and active cerebrovascular pressure reactivity both PAR and sCVR increased and during hypoxia, a passive tension condition, both resistances decreased in response to pressor challenge. In this study, measured values of PAD ranged from 30 μ m to 70 μ m which corresponds to a range of resistance of 6665 mmHg/ml/min to 225 mmHg/ml/min. Because the arterioles play a major role in the control of CBF such a range of high resistance value is to be expected. In contrast, model-derived values of cerebrovascular resistance of the physiologically based biomechanical model of cerebrovascular pressure transmission derived from ABP and ICP recordings during baseline ranged from 2.2 mmHg/100 gm/min to 3.5 mmHg/100 gm/min. Because the model-derived value of cerebrovascular resistance represents the resistance of the cerebral arterial vascular tree and capillaries with large cross sectional area incredibly rich in parallel pathways, the overall value of equivalent resistance should be several orders of magnitude less than that of a single arteriole. Since hypoxia induces relatively uniform vasodilation the entire arterial-arteriolar bed, both pial arteriolar resistance and cerebrovascular resistance should similarly decrease. Furthermore, the nature of the pressor challenge is that it also uniformly changes the resistance of pial arterioles, during active vasoreactivity resistance increases and during passive vasoreactivity resistance decreases. Here again, changes in the resistance of the entire cerebral arterial-arteriolar tree should follow the corresponding changes in arteriolar resistance. Thus, our findings of no intra-group differences but significant inter-group changes in the mean values of percent change of PAR and sCVR of the biomechanical model are reasonable.

Starting over two decades ago system analysis techniques were first applied in laboratory studies designed to describe the black box transfer function between arterial blood pressure and intracranial pressure (14-17). Changes in the spectral characteristic of the transfer function were observed to occur with manipulations of either vascular or extracellular fluid volume within the craniospinal sac. Increased cerebral blood volume induced by vasodilation resulted in an increased gain in both low frequency and high frequency components of the pressure transmission frequency characteristics (17). Using both time and frequency domain approaches in which an approximated white noise input was induced by randomization of the arterial pressure pulses one study concluded that the pressure transmission characteristic of the adult dog demonstrated a resonance (18). A clinical study of the cerebrovascular pressure transmission characteristics of thirty brain-injured patients found that 40% of the patients also demonstrated a resonance property (19). In contrast, to the numerical black-box approaches of previously studies, this study employed a two step design procedure to specifically evaluate cerebrovascular resistance, a critical parameter of cerebral circulation. In the first step a black box system identification technique is used to define cerebrovascular pressure transmission based the dynamic relationship between ABP and ICP of a previously proposed biomechanical model (20). The products of this first step are the modal frequencies which describe the modes of energy transfer of cerebrovascular pressure transmission. In the second procedural step these modes are coupled with the ABP and ICP recordings to identify the optimal parameter value of cerebrovascular resistance for each recording interval.

Recent published guidelines for the management of patients with severe traumatic brain injury state prescribe the maintenance of a general threshold of cerebral perfusion pressure (CPP) of 60 mmHg during intensive care monitoring of arterial blood pressure (ABP) and intracranial pressure (ICP) [21]. This threshold value of CPP is near the critical threshold for ischemia, the lower limit of unimpaired autoregulation, which is generally thought to be between 50-60 mmHg [22]. However, the insult of brain trauma may alter autoregulation of cerebral blood flow (CBF) by elevating the critical ischemic threshold above 60 mmHg and thereby resulting in the risk of inducing ischemia by management. On the other hand artificial elevation of CPP to greater than 70 mmHg increases the risk of adult respiratory distress syndrome [23]. Given these risks, the guidelines point out the need for the development of minimally invasive methods designed to assess the relationship between CPP and autoregulation and between ischemia and CPP [21]. Such methods could be used to individualize patient CPP management and minimize secondary complications associated with traumatic brain injury [21]. This study demonstrates that percent changes in model-derived cerebrovascular resistance correspond to changes in pial arteriolar resistance induced by increased CPP in response pressor challenge. Thus, assessments of relative changes of CVR and CBF could be used as an ancillary methodology to assist in setting the optimal management CPP for a given patient. Retrospective analyses of clinical pressure recordings support such a potential. Application of the modeling methodology to pressure recordings obtained from traumatic brain-injured patients that demonstrated either plateau waves (24) or intractable intracranial hypertension (24) and stroke patients with subarachnoid hemorrhage (25) found that the changes in both sCVR and sCBF were consistent with corresponding accepted changes in the underlying pathophysiology. Specifically, consistent with the descriptive vasodilatory/vasoconstrictive cascade model of a plateau wave (26) sCVR was found to decrease during a plateau wave and increase following the wave (24). During intractable intracranial hypertension sCVR was found to progressively increase (24). Such findings suggest the occurrence of cerebrovascular compression as CPP falls below the lower limit of autoregulation. Finally from pressure recordings obtained from patients with aneurismal stroke, sCVR progressively increased in patients who experienced a poor outcome; whereas, in those patients who experienced a good outcome, sCVR progressively decreased during the monitoring period (25).

Caution should be used in the application of the proposed methodology. The characteristics of cerebrovascular pressure transmission are primarily dependent on the vascular tone of the arterial-arteriolar bed. The derived values of cerebrovascular resistance and cerebral blood flow are global assessments; thus, such assessments may be limited to either laboratory conditions or brain injuries that tend to uniformly affect the cerebral microvasculature as previously described (20-23). It seems unlikely that the modeling method would work well to detect localized losses of autoregulation as may be associated with focal ischemia or hemorrhage. Initially, laboratory studies designed to directly compare experimental values of cerebrovascular resistance and cerebral blood flow to model-derived cerebrovascular resistance and cerebral blood flow from animal models of diffuse axonal injury using fluid percussion injury (27) and subarachnoid hemorrhage (28) need to be done. Later laboratory studies on the use of the methodology on laboratory models such as ischemic stroke (29) or altered intracranial volume pressure dynamics (30) should also be done. Once verification of the accuracy of model-derived cerebrovascular resistance is demonstrated in each laboratory model then initial corresponding clinical studies in which routine monitoring of arterial blood pressure and intracranial pressure could be designed to further verify the methodology and evaluate its potential use in patient management.

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Figure 1. Second Step of Modeling Method: Simulation of ICP with Biomechanical Model

a) Arterial Blood Pressure Recording. The ABP recording for each 8s epoch is applied as input to biomechanical model. **b) Biomechanical Model.** **c) Simulated ICP Recording.** Parameters of the model are manipulated to obtain an optimal set which minimizes the least squares difference between: 1) the modal frequencies of cerebrovascular pressure transmission derived in Step 1 and those of the biomechanical model and 2) the actual and simulated ICP recordings. **d) Actual ICP Recording.**

Figure 2. Percent Change of Pial Arteriolar Resistance and Model-Derived Cerebrovascular Resistance versus Percent Change of Cerebral Perfusion Pressure

a) Normoxic Control Group. Both percent change of pial arteriolar resistance (%ΔPAR), striped bar, and percent change of model-derived cerebrovascular resistance (%ΔsCVR), black bars, increased with an increase of percent change of cerebral perfusion pressure (%ΔCPP) indicative of intact cerebrovascular pressure regulation. B) Hypoxic Treated Group. Both %ΔPAR, striped bar, and %ΔsCVR, black bar, decreased with an increase of %ΔCPP indicative of impaired regulation of cerebral blood flow (CBF).

Table 1

Grand Mean Values (+/-S.E.M.) Arterial Blood Pressure (ABP), Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), Arterial Blood pH, Arterial Blood Partial Pressure of Carbon Dioxide (pCO2) and Oxygen (pO2) for Normoxia, Hypoxia, and Challenge Conditions.

Condition	N	ABP (+/-S.E.M.) mmHg	ICP (+/-S.E.M.) mmHg	CPP (+/-S.E.M.) mmHg	pH (+/-S.E.M.)	pCO2 (+/-S.E.M.) mmHg	pO2 (+/-S.E.M.) mmHg
Control Group							
Normoxia Baseline	5	84.5 (2.6)	5.5 (0.9)	79.8 (1.5)	7.36 (0.8)	35 (3.5)	97 (2.8)
Pressor Challenge During Normoxia	5	101.3 (2.7) ¹	3 (0.6) ¹	98 (2.5) ¹			
Hypoxic Group							
Hypoxia Baseline.	5	86.8 (2.1)	2.8 (0.5)	82.7 (0.65)	7.39 (0.5)	37 (2.5)	45 (1.2) ²
Pressor Challenge during Hypoxia	5	102.7 (3.5) ¹	9.5 (1.5) ¹	93.6 (1.9) ¹			

¹ Denotes a significant degree of difference between baseline and challenge mean values at level of p<0.005

² Denotes a significant degree of difference between baseline mean values between the two groups at level of p<0.005

Table 2

Grand Mean Values (+/-S.E.M.) Pial Arteriolar Diameter (PAD), Pial Arteriolar Resistance (PAR), and Model-Derived Cerebrovascular Resistance (sCVR) of Cerebrovascular Pressure Transmission

Condition	N	PAD (+/-S.E.M.)	PAR (+/-S.E.M.)	sCVR (+/-S.E.M.)
		um	mmHg/ml/min	mmHg/ml/100 gm/min
Control Group				
Normoxic Baseline	5	64.6 (1.2)	310.3 (45.6)	2.5 (0.6)
Pressor Challenge during Normoxia	5	57.4 (2.1) ¹	519.1 (56.5) ¹	3.9 (0.10) ¹
Hypoxic Group				
Hypoxic Baseline.	5	65.6 (3.4)	306.9 (99.3)	3.01 (0.8)
Pressor Challenge during Hypoxia	5	75.7 (2.9) ¹	173.1 (35.4) ²	1.81 (0.4) ²

¹Denotes a significant degree of difference between baseline and challenge mean values at level of p<0.005

²Denotes a significant degree of difference between baseline and challenge mean values at level of p<0.025