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Model Derived Assessment of Cerebrovascular Resistance and Cerebral Blood Flow Following Traumatic Brain Injury

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Abstract

Published guidelines point out the need for the development of methods that individualize patient cerebral perfusion management and minimize secondary ischemic complications associated with traumatic brain injury. A laboratory method has been developed to determine model-derived assessments of cerebrovascular resistance (mCVR) and cerebral blood flow (mCBF) from cerebrovascular pressure transmission, the dynamic relationship between ABP and ICP [3]. The aim of this twofold study is to: 1) evaluate relative changes in the model-derived parameters of mCVR and mCBF with the corresponding changes in the pial arteriolar vascular parameters of pial arteriolar resistance (PAR) and relative pial arteriolar blood flow (rPABF); and 2) examine the efficacy of the proposed modeling methodology for continuous assessment of the state of cerebrovascular regulation by evaluating relative changes in the model-derived parameters of cerebral blood flow and cerebrovascular resistance in relation to changes of cerebral perfusion pressure prior to and following fluid percussion brain injury.

Changes of arterial blood pressure (ABP), intracranial pressure (ICP), pial arteriolar resistance (PAR), relative arteriolar blood flow (rPABF), and the corresponding model derived parameters of mCBF and mCVR induced by acute hypertensive challenge were evaluated before and following fluid percussion injury in piglets equipped with cranial windows.

Before fluid percussion hypertensive challenge resulted in a significant increase of PAR and mCVR; whereas, both rPABF and mCBF remained constant. Following fluid percussion, hypertensive challenge resulted in a significant decrease of PAR and mCVR and consistent with impaired cerebrovascular regulation. Hypertensive challenge significantly increased both rPABF and mCBF and approximately doubled with increased CPP with correlation values of ($r=0.96$, $p<0.01$) and ($r=0.97$, $p=0.01$) respectively. Assessment of model-derived cerebrovascular resistance and cerebral blood flow with changes of CPP provides a means to continuously monitor the state of cerebrovascular regulation.

Keywords

cerebrovascular resistance; cerebral blood flow; traumatic brain-injury

INTRODUCTION

Recently published guidelines for the intensive care management of adult patients with traumatic brain injury 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) [1]. This threshold value of CPP is near the critical threshold for ischemia, the lower limit of unimpaired cerebrovascular regulation for adults, which is generally thought to be between 50-60 mmHg [2]. However, brain trauma may injure cerebrovascular pathways of the arterial/arteriolar bed and alter regulation of cerebral blood flow (CBF) by elevating the lower limit of regulation above 60 mmHg. For such a situation maintenance of CPP at 60 mmHg could result in decreased CBF, and cerebral ischemic complications. On the other hand, artificial elevation of CPP to greater than 70 mmHg increases the risk of adult respiratory distress syndrome [3]. Given these risks, the guidelines point out the need for the development of methods that individualize intensive care management and minimize secondary complications associated with traumatic brain injury [1].

The need for an intensive care bedside methods designed to monitor the state of cerebrovascular regulation is further emphasized when intensive care management of brain injured pediatric patients is considered. Because of continuous growth there are major differences between the cerebrovascular regulatory ranges of an infant and that of a teenager [6]. Multiple age-specific lower limits of regulation for pediatric population do not exist [6]. Here again, an intensive care monitoring method designed to continuously evaluate cerebral blood flow and cerebrovascular resistance as a means to assess the state of cerebrovascular regulation is needed. Such a bedside method could be integrated with other multi-modal monitoring techniques to develop an individualized management strategy for each brain injured pediatric patient.

Recently, we have developed a method to determine model-derived assessments of cerebrovascular resistance (mCVR) and cerebral blood flow (mCBF) from cerebrovascular pressure transmission, the dynamic relationship between ABP and ICP [4–5]. The aim of this study is twofold: 1) compare relative changes in the model-derived parameters of mCVR and mCBF with corresponding changes of pial arteriolar resistance (PAR) and relative pial arteriolar blood flow (rPABF); and 2) examine the efficacy of the proposed modeling methodology for continuous assessment of the state of cerebrovascular regulation by evaluating relative changes in the model-derived parameters and experimentally-derived pial arteriolar vascular parameters in relationship to changes cerebral perfusion pressure induced by hypertensive challenge prior to and following fluid percussion brain injury (FPI).

MATERIALS AND METHODS

Laboratory Materials and Manipulations

The Animal Care and Use Committees of both The University of Tennessee Health Science Center and The University of Memphis approved the protocol for this study. This study is an application of an analytical modeling method on recordings of ICP and ABP obtained from preparations described in a previous published report [6]. Briefly, each animal was intramuscularly administered ketamine (33 mg/kg) and acepromazine (3 mg/kg). Six piglets ranging in weight from 1.8 to 3.3 kg were intubated and ventilated with a positive pressure

respirator (Inter MED Bear BP 200 Infant Pressure Ventilator, Riverside, CA). Periodic assessments of the partial pressures of carbon dioxide and oxygen and of pH, and hemoglobin in arterial blood as measured by Instrumentation Laboratory 1306, pH/Blood Gas Analyzer (Lexington, MA) were made and used to guide ventilation to maintain normal blood gas levels and pH at about 30 mmHg Pco₂, greater than 85 mmHg Po₂, and 7.35 pH. Hemoglobin varied between 12 and 16 g/dl across all preparations. Rectal temperature of animals was maintained at 38° C. A 2 cm in diameter cranial window was placed over the left parietal cortex and secured with dental acrylic. The space under the window was filled with artificial cerebrospinal fluid through stainless steel injection ports incorporated into the sides of the window. Hypertensive challenge was accomplished by infusing norepinephrine (1ug/kg/min) into the femoral vein over a period of five minutes. Time of administration of norepinephrine following percussion ranged from 17 min to 93 min with a mean $\pm$ S.E.M. of 39.3 $\pm$ 5.2 min. The previously described FPI apparatus [6] was used to deliver a mean impact $\pm$ S.E.M. of approximately 3.5 $\pm$ 0.17 atm. Model-derived parameter changes to induced hypertensive challenge were measured before and after percussion injury.

The methods to determine pial arteriolar diameter (PAD) and pial arteriolar resistance (PAR) have been described previously [4–5]. Briefly, a videomicrometer with magnification of 3600X was used to image three arterioles which were videotaped during the experiment. The video recording was then converted to still-image frames at 30 frames/sec using OSS Video Decompiler software (One Stop Soft Inc, www.onestopsoft.com). A tracking algorithm was implemented using MATLAB software (The MathWorks Inc., Natick, MA) to measure the pial arteriolar diameter (PAD). Mean PAD values were computed over 4 min during periods of continuous steady-state conditions. Based on the biomechanics of steady-state laminar flow in a cylindrical tube [7], the resistance of a pial arteriole can be estimated as:

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

Pial arteriolar resistance (PAR) based on a 1 mm length was computed using the coefficient of viscosity for whole blood as 0.0027 N-s/m² at 37 C°. Relative pial arteriolar blood flow (rPABF) was estimated as:

$$\text{rPABF} = \text{CPP} / \text{PAR} \quad (2)$$

Because the value of CPP in this calculation is much higher than the actual value of transverse pressure across the pial arterioles [8–9] the computed value of rPABF is much higher than the actual value of flow and therefore represents a relative estimate of flow.

Intraparenchymal ICP recordings obtained with a Camino Direct Pressure Monitor (Camino Laboratories, San Diego, CA) and femoral ABP recordings obtained with a SpaceLabs Model 90623A Monitor (SpaceLabs Inc., Redmond, WA) were digitized at 250 Hz as previously described [4–5]. Cerebral perfusion pressure (CPP) was computed as the difference between ABP and ICP.

The first step of a two-step modeling method uses system identification modeling the details of which have been previously reported (6). The physiologically-based biomechanical model proposed by Czosynka and his colleagues [10] is used to provide a generalized dynamic differential equation of cerebrovascular pressure transmission, the dynamic relationship between ABP and ICP (see Fig. 1). Application of system identification modeling to this equation produces a simulated ICP recording that matches the actual ICP recording by minimization of the least squares difference between the actual and simulated ICP [11]. This initial modeling step enables the determination of the modal frequencies of cerebrovascular

pressure transmission for each 8s modeling period. For the brief 8s 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 modeling step the values of the modal frequencies derived by the first step numerical model and the corresponding ABP recording are used to determine the parameters of the physiologically-based biomechanical model. Specifically, MATLAB software was used to simulate the biomechanical model using a state variable description of the biomechanical model previously reported [10]. During the computation the resistance and compliance elements of the biomechanical model were manipulated such that the minimum square error for the 8s recording interval between: 1) the actual and simulated ICP recordings and 2) the numerical model-derived modal frequencies and those of the biomechanical value of were obtained.

Values of each element of the biomechanical model were manipulated. Initially a normal CBF was assumed to be 40ml/100g/min [12–13]. Both compliance and resistance elements were allowed to range over values consistent with those reported in previously published modeling studies of intracranial pressure dynamics [10, 13–14]. A maximum mean squared error of 0.6 which results in a goodness of fit in which the mean maximum difference between the actual and simulated ICP recordings was less than 0.6 mmHg for each point was required. Also, the minimum correlation value of 0.9 between both actual and simulated ICP recording was used to initialize the square error values. All mean values are reported with $\pm$ standard error of mean values. In all cases, the degree of significance between the difference of two mean values was determined by using the t-statistic.

RESULTS

For the four minute periods during both baseline and hypertensive steady-state conditions mean values of PAR, mCVR, rPABF, and mCBF before and after FPI are given (see Table 1). Prior to FPI hypertensive challenge produced a significant increase of the means of ABP, CPP, PAR, and mCVR while both mean ICP and PAD decreased and mean rPABF and mCBF remained relatively constant. Following FPI hypertensive challenge significantly increased the mean values of ABP, ICP, CPP, rPABF and mCBF with both mean rPABF and mCBF more than doubling in value. In addition the mean values of both PAR and mCVR significantly decreased (see Table 1).

Grand mean values of model-derived and experimentally-derived parameters during baseline and hypertension of mCVR, PAR, rPABF, and mCBF before and after percussion injury are shown (see Fig. 2). Consistent with functional cerebrovascular regulation of the uninjured preparations, hypertensive challenge resulted in direct relationships between mCVR and CPP and PAR and CPP (see Fig 2a, 2b). Also for this condition, rPABF and mCBF remained relatively constant with changes of CPP (see Fig. 2c, 2d). After induction of brain-injury, hypertensive challenge resulted in strong inverse relationship between both mCVR and CPP ($r=-0.87$, $p=0.01$) and PAR and CPP ($r=-0.78$, $p=0.01$) (see Fig. 2e, 2f). Also for this condition direct relationships between both mCBF and CPP ($r=0.97$, $p=0.01$) and rPABF and CPP ($r=0.96$, $p=0.01$) were determined (see Fig. 2g, 2h). Moreover, during the hypertensive state both mCBF and rPABF were nearly double the flow values determined for hypertensive state prior to percussion injury. Correlations of mean values ($n=24$) between PAR and mCVR and between rPABF and mCBF were strong at ($r=0.71$, $p=0.01$) and ($r=0.94$, $p=0.01$) respectively.

Variations of CPP of 2 mmHg to 4 mmHg occur during steady-state conditions. To characterize the influence of these steady-state pressure variations on each circulatory

parameter the slopes of the regression line parameter, $\Delta\text{PAR}/\Delta\text{CPP}$, $\Delta\text{mCVR}/\Delta\text{CPP}$, $\Delta\text{rPABP}/\Delta\text{CPP}$, and $\Delta\text{mCBF}/\Delta\text{CPP}$ were determined for continuous 4 min steady state baseline and hypertensive challenge conditions (see Table 2). Before FPI variation of both mean $\Delta\text{PAR}/\Delta\text{CPP}$ and $\Delta\text{mCVR}/\Delta\text{CPP}$ were positive during baseline and significantly increased during the challenge condition indicative of intact cerebrovascular regulation. For this condition both $\Delta\text{rPABP}/\Delta\text{CPP}$ and $\Delta\text{mCBF}/\Delta\text{CPP}$ remained relatively constant. After FPI both mean $\Delta\text{PAR}/\Delta\text{CPP}$ and $\Delta\text{mCVR}/\Delta\text{CPP}$ were negative and decreased significantly during hypertensive challenge while the changes of both $\Delta\text{rPABP}/\Delta\text{CPP}$, and $\Delta\text{mCBF}/\Delta\text{CPP}$ were positive and significantly increased during challenge (see Table 2).

DISCUSSION

The new findings of this study are that changes of model-derived assessments of cerebrovascular resistance and cerebral blood flow have the potential to provide continuous bedside assessment of the state of cerebrovascular regulation and cerebral perfusion. Prior to percussion injury changes of both the model-derived and experimentally derived parameters of cerebral circulation induced by hypertensive challenge were consistent with intact regulation. Both pial arteriolar resistance and model-derived mCVR increased with CPP while pial arteriolar blood flow and model-derived mCBF remained relatively constant. For this condition steady-state changes of PAR and mCVR were directly proportional to variations in CPP. In contrast following percussion injury changes of the experimental and model-derived parameters of circulation were consistent with impaired regulation. Induced hypertensive challenge resulted in a significant decrease of both pial arteriolar resistance and model-derived CVR with increasing CPP, while both rPABF and mCBF increased significantly. For this condition steady-state variations of PAR and mCVR were inversely proportional to variations in CPP.

Monitoring the relationship between CPP and the model-derived parameters of mCVR and mCBF provides a potential method for the continuous evaluation of cerebrovascular regulation and cerebral perfusion. Such evaluations could be used to customize the management of a patient with brain injury. During intact cerebrovascular autoregulation the slope of the regression line parameter, $\Delta\text{mCVR}/\Delta\text{CPP}$, is positive with respect to changes of CPP. In contrast, during loss of autoregulation the slope of the line is negative. Using these criteria, the proposed methodology has specificity of 100% and a sensitivity of 100% (see Table 2). Of note is that this continuous assessment of cerebrovascular regulation does not require manipulation of CPP but is based on steady-state variations that naturally occur during management. In addition, the level of perfusion determined by mCBF may be a useful management parameter. During the management of either adults or pediatric patients where the age related lower limits of regulation are generally unknown it could be used to prevent either excessive or insufficient perfusion.

Possible limitations of the proposed methodology and interpretation of our results should be noted. First, because experimental absolute measures of cerebrovascular resistance and cerebral blood flow were not done in this study assessment only of relative changes of CVR and CBF could be made. Verification of modeling methodology is based on a comparison of the close similarity of correlations of both pial arteriolar resistance and blood flow and the corresponding model-derived values of mCVR and mCBF with CPP during both intact and impaired cerebrovascular regulation. However, the model-derived values of mCVR and mCBF are in reasonable agreement with previously published absolute experimental values of CBF and CVR obtained for the piglet [15–18]. At baseline for the group of uninjured piglets average total volumetric flow was 11.4 ml/min. Assuming an average piglet brain weight of 25 g then tissue flow was approximately 45.6 ml/100g/min with a cerebrovascular resistance of approximately 1.4 mmHg/ml/100g/min. Studies using anesthetized newborn

piglets reported a control CBF values that range from 38 ml/100g/min to 70 ml/100g/min [15–18]. Further experiments designed to directly validate the accuracy of the parameter identification modeling method by directly comparing model-derived estimates with absolute measurements of CBF and CVR are needed.

Secondly, use of the methodology may be limited by the nature of brain-injury. The experiments used a fluid percussion injury piglet model that has been previously shown to demonstrate characteristics of diffuse brain injury [19]. Since the pulsation characteristics of the ICP recording are dependent on the vascular tone of arterial-arteriolar bed [17], the proposed methodology maybe limited to brain-injuries that involve generalized diffuse injury to cerebral arteriolar vascular bed or least large proportions of the total cerebral vasculature. These methods would not detect effects small focal injuries on localized loss of vascular control. However, in such cases, most of the cerebral vasculature would be well regulated and consistent findings of intact regulation using model-derived CBF and CVR.

The findings of the present study indicate that relative changes of two critical parameters of cerebral circulation, model-derived cerebrovascular resistance and cerebral blood flow, can be used to monitor the state of cerebrovascular regulation and cerebral perfusion. The ability to continuously monitor these critical circulatory parameters has the potential to assist in tailoring the intensive care management of CPP to each brain-injured patient. At present conclusions of this study are only known to be applicable to percussion injury obtained from an animal model with characteristics of diffuse axonal injury [19]. Further experimentations using other situations or experimental pathologies need to be performed to investigate general applicability of the method.

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a) Model of Cerebrovascular Pressure Transmission

b) Step 1 Numerical System Identification Modeling

c) Step 2 Parameter Variation of State Variable Model

Figure 1. Two-Step Modeling Method of Cerebrovascular Pressure Transmission

a) Biomechanical Model of Cerebral Hemodynamics. Previously proposed physiologically-based biomechanical model [10], was used to define the dynamic analytical relationship between ABP and ICP. b) Step 1: Numerical System Identification Modeling: Using the actual ABP and ICP recordings and the biomechanical model of cerebrovascular pressure transmission, a system identification autoregressive moving average technique [11] is used to produce a simulated ICP output that matches the actual ICP recording and provides the modal frequencies of the cerebrovascular pressure transmission. c) Step 2: Parameter Variation of State Variable Model: Resistance and compliance parameters of the state variable model were manipulated such that the minimum square error between: 1) the actual

and simulated ICP recordings; and 2) the modal frequencies of the system identification model and state variable model was obtained.

Figure 2. Model-Derived Parameters of mCVR, mCBF, PAR and rPABF with Increased Cerebral Perfusion Pressure Induced by Hypertensive Challenge Before and After Fluid Percussion Injury

Before FPI: a) mCVR and b) PAR. Model-derived mCVR and PAR increased directly with increasing CPP. c) mCBF and d) rPABF. Model-derived mCBF and rPABF remained relatively constant with increased CPP. After FPI: e) mCVR and f) PAR. Model-derived mCVR and PAR decreased with increased CPP and were lower than the corresponding assessments prior to FPI. g) mCBF and h) rPABF. Model-derived mCBF and rPABF increased with increased CPP. During hypertension challenge both assessments of blood

flow were two to three times higher than corresponding assessments prior to FPI. Solid line represents regression line of plotted data points. Value of S.E.M. is within each symbol.

Changes of Mean ($\pm$ S.E.M.) ABP, ICP, CPP, mCVR, mCBF, PAD, PAR and rPABF in Response to Norepinephrine Challenge Before and Following Fluid Percussion Injury

Table 1

	N	ABP (mmHg)	ICP (mmHg)	CPP (mmHg)	mCVR (mmHg/ml/min)	mCBF (ml/min)	PAD (μ m)	PAR (mmHg/ml/min)	rPABF (ml/min)
						Before FPI			
Base	6	66.8 [*] (± 0.25)	4.2 [*] (± 0.03)	62.6 [*] (± 0.13)	5.5 [*] (± 0.07)	11.4 [†] (± 0.1)	57.8 [*] (± 0.03)	543.2 [*] (± 10.7)	0.12 (± 0.01)
Chal.	6	83.7 [‡] (± 0.75)	2.8 (± 0.1) [‡]	80.8 (± 0.8) [‡]	7.9 ($\pm .07$) [‡]	10.3 (± 0.01)	52.1 (± 0.5) [§]	826.1 (± 14.5) [‡]	0.10 (± 0.01)
						After FPI			
Base	6	53.4 [*] (± 0.7)	5.1 [*] (± 0.03)	50.2 (± 1.2)	4.0 [*] (± 0.1)	12.5 [†] (± 0.3)	64.3 [*] (± 1.6)	351.7 [*] (± 46.6)	0.14 (± 0.0001)
Chal.	6	87.4 (± 0.8) [‡]	8.8 (± 0.7) [‡]	78.6 (± 0.7) [‡]	2.8 ($\pm .03$) [‡]	26.5 (± 0.2) [‡]	87.2 (± 0.5) [‡]	94.3 (± 1.9) [‡]	0.84 ($\pm .0003$) [‡]

^{*} Denotes degree of significance between baseline prior to FPI and baseline after FPI at $p < 0.001$.

[†] Denotes degree of significance between baseline prior to FPI and baseline after FPI at $p < 0.005$.

[‡] Denotes degree of significance between baseline and challenge mean values at $p < 0.001$.

[§] Denotes degree of significance between baseline and challenge mean values at $p < 0.005$.

Table 2

Grand Mean($\pm$ S.E.M.) Regression Line Slopes of Δ PAR, Δ mCVR, Δ rPBF, and Δ mCBF with Respect to Δ CPP During Steady-State Baseline and Hypertensive Challenge Conditions Before and Following FPI.

	N	Before FPI				After FPI			
		Δ PAR/ Δ CPP (mmHg/mm l/min/mm Hg)	Δ mCVR/ Δ CPP (mmHg/ ml/min/ mmHg)	Δ rPBF/ Δ CPP (ml/min/ mmHg)	Δ mCBF/ Δ CPP (ml/min/ mmHg)	Δ PAR/ Δ CPP (mmHg/mm l/min/mm Hg)	Δ mCVR/ Δ CPP (mmHg/ ml/min/ mmHg)	Δ rPBF/ Δ CPP (ml/min/ mmHg)	Δ mCBF/ Δ CPP (ml/min/ mmHg)
Base	6	2.56 (± 0.16)	0.21 (± 0.010)	0.0078 (± 0.0001)	0.018 (± 0.002)				
Chal.	6	6.71 (± 0.18) [†]	0.44 (± 0.09) [†]	0.0086 (± 0.0001) [†]	0.021 (± 0.001)				
Base	6	-3.07 [*] (± 0.06)	-0.19 [*] (± 0.005)	0.11 [*] (± 0.01)	0.36 [*] (± 0.02)				
Chal.	6	-9.12 (± 0.24) [†]	-0.67 (± 0.03) [†]	0.20 (± 0.002) [†]	1.49 (± 0.05) [†]				

* Denotes degree of significance between baseline prior to FPI and baseline after FPI at p<0.001.

† Denotes degree of significance between baseline and challenge conditions at p<0.001.