Original Research

Model-derived assessment of cerebrovascular resistance and cerebral blood flow following traumatic brain injury

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Abstract

The 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, and the dynamic relationship between arterial blood pressure (ABP) and intracranial pressure (ICP). The aim of this two-fold 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 CBF and cerebrovascular resistance in relation to changes of cerebral perfusion pressure prior to and following fluid percussion brain injury. Changes of ABP, ICP, 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, which approximately doubled with increased CPP with correlation values of $r = 0.96$ ($P < 0.01$) and $r = 0.97$ ($P \leq 0.01$), respectively. The assessment of model-derived cerebrovascular resistance and CBF with changes of CPP provides a means to monitor continuously the state of cerebrovascular regulation.

Keywords: cerebrovascular resistance, cerebral blood flow, traumatic brain injury

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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 and 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 method 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

*Deceased

a teenager.[4] Multiple age-specific lower limits of regulation for pediatric population do not exist.[4] Here again, an intensive care monitoring method designed to evaluate continuously CBF and cerebrovascular resistance as a means to assess the state of cerebrovascular regulation is needed. Such a bedside method could be integrated with other multimodal 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 CBF (mCBF) from cerebrovascular pressure transmission, the dynamic relationship between ABP and ICP.[5,6] The aim of this study is two-fold: (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 of CPP 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.[4] Briefly, each animal was intramuscularly administered ketamine (33 mg/kg) and acepromazine (3 mg/kg). Six male piglets between two and three weeks old, 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, USA). 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, USA) were made and used to guide ventilation to maintain normal blood gas levels and pH at about 30 mmHg PCO_2, greater than 85 mmHg PO_2 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-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 (150 mEq Na^+/L, 3 mEq K^+/L, 2.5 mEq Ca^{2+}/L, 1.2 mEq Mg^{2+}/L, 132 mEq Cl^-/L, 3.7 mmol/L glucose, 6 mmol/L urea and 25 mEq HCO_3^-/L with typically pH 7.33, 6.1 kPa PCO_2, 5.7 kPa PO_2) through the stainless-steel injection ports incorporated into the sides of the window. Hypertensive challenge was accomplished by infusing norepinephrine (1 μg/kg/min) into the femoral vein over a period of five minutes. The time of administration of norepinephrine following percussion ranged from 17 to 93 min with a mean $\pm$ standard error of mean (SEM) of 39.3 ± 5.2 min. The previously described FPI apparatus[4] was used to deliver a mean impact $\pm$ SEM of 3.5 ± 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 PAR have been described previously.[5,6] Briefly, a videomicrometer with magnification of 3600× was used to image three arterioles that were videotaped during the experiment. The video recording was then converted to still-image frames at 30 frames/s 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, USA) to measure the PAD. Mean PAD values were computed over four minutes 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:

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

PAR based on a 1 mm length was computed using the coefficient of viscosity for whole blood as 0.0027 N-s/m^2 at 37°C. rPABF was estimated as

$$\mathrm{rPABF} = \mathrm{CPP}/\mathrm{PAR} \qquad (2)$$

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, USA) in the same hemisphere as the pial window and femoral ABP recordings obtained with a SpaceLabs Model 90623A Monitor (SpaceLabs Inc, Redmond, WA, USA) were digitized at 250 Hz as described previously.[5,6] 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 reported previously.[4] 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, and the dynamic relationship between ABP and ICP (see Figure 1). The 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 eight-second modeling period. For the brief eight-second 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.

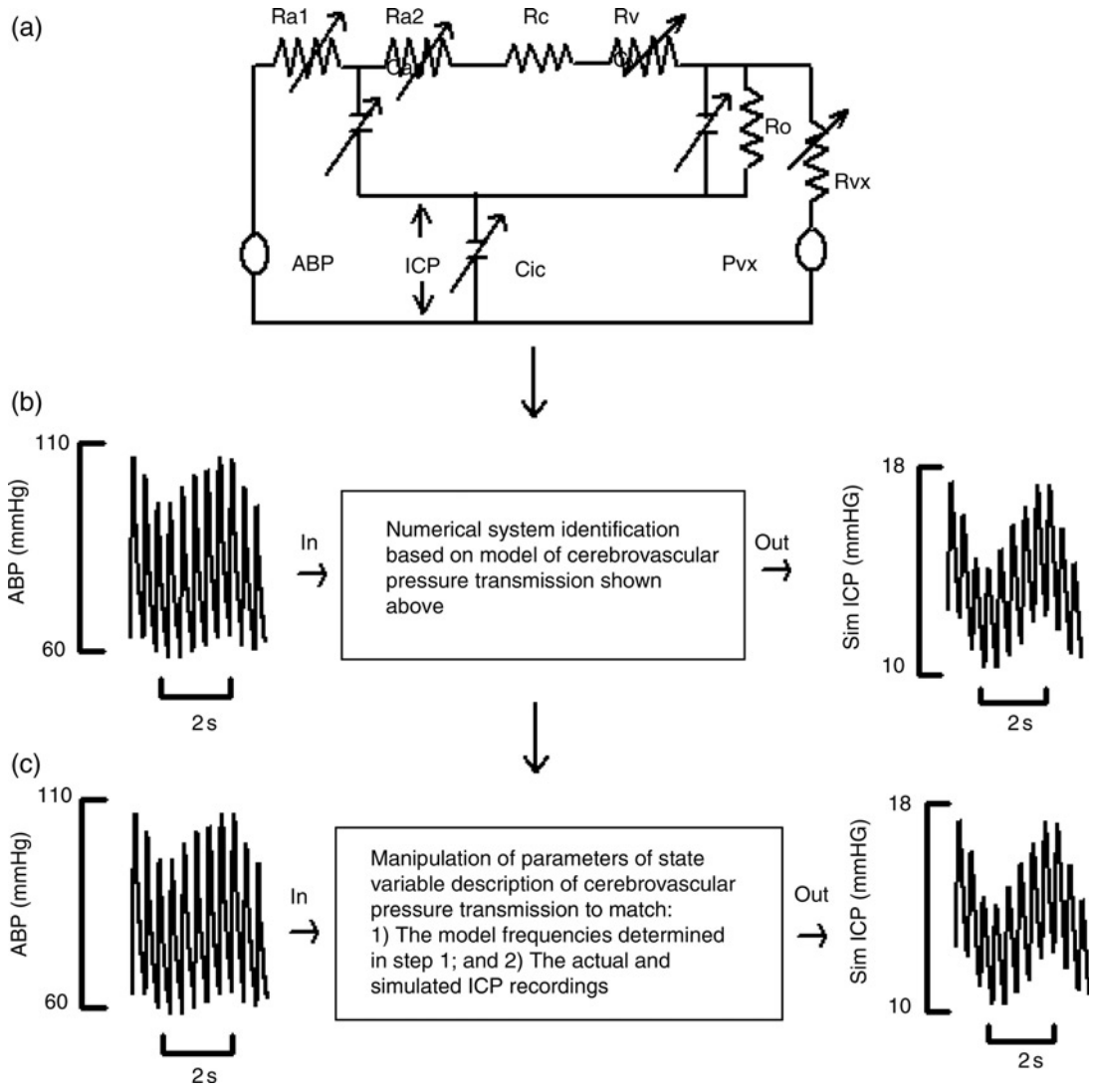

Figure 1 Two-step modeling method of cerebrovascular pressure transmission. (a) Biomechanical model of cerebral hemodynamics. Previously proposed physiologically based biomechanical model[10] was used to define the dynamic analytical relationship between ABP and ICP. (b) Step 1: Numerical system identification 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. ABP, arterial blood pressure; ICP, intracranial pressure; SEM, standard error of mean

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 reported previously.[10] During the computation, the resistance and compliance elements of the biomechanical model were manipulated such that the minimum square error for the eight-second recording interval between (1) the actual and simulated ICP recordings and (2) the numerical model-derived modal frequencies and those of the biomechanical value were obtained.

Values of each element of the biomechanical model were manipulated. Initially a normal CBF was assumed to be 40 mL/100 g/min.[12,13] Both compliance and resistance elements were allowed to range over values consistent with those reported in previously published modeling studies of ICP 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 $\pm$SEM values. In all cases, the degree of significance between the differences of two mean values was determined by using the *t*-statistic.

Results

Both baseline and hypertensive steady-state conditions mean values of PAR, mCVR, rPABF and mCBF before

and after FPI were calculated on 30 eight-second values obtained over the four-minute recording period. The grand mean of each of these parameter values based on all six animals is 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 ($n = 12$) 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 Figure 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 Figures 2a and b). Also for this condition, rPABF and mCBF remained relatively constant with changes of CPP (see Figures 2c and d). After induction of brain injury, hypertensive challenge resulted in strong inverse relationship between both mCVR and CPP ($r = -0.87$, $P \leq 0.01$, $n = 12$) and PAR and CPP ($r = -0.78$, $P \leq 0.01$, $n = 12$) (see Figures 2e and f). Also for this condition direct relationships between both mCBF and CPP ($r = 0.97$, $P \leq 0.01$, $n = 12$) and rPABF and CPP ($r = 0.96$, $P \leq 0.01$, $n = 12$) were determined (see Figures 2g and h). Moreover, prior to FPI the correlation between PAR and mCBF was $r = 0.42$ ($n = 12$) and following FPI this correlation was $r = 0.77$ ($P \leq 0.01$, $n = 12$). A similar pattern of weak correlations before FPI and significant robust correlations following FPI existed for the relationship between mCBF and rPABF and PAR and mCVR. For the relationship between mCBF and rPABF, these correlations were $r = 0.14$ ($n = 12$) prior to FPI and $r = 0.92$ ($P \leq 0.01$, $n = 12$) following FPI. For the relationship between PAR and mCVR, these correlations were $r = 0.27$ ($n = 12$) and $r = 0.74$ ($P < 0.01$, $n = 12$) before and after FPI, respectively.

Variations of CPP of 2–4 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, ΔPAR/ΔCPP, ΔmCVR/ΔCPP, ΔrPABP/ΔCPP and ΔmCBF/ΔCPP, were calculated based on the eight-second parameter values ($n = 30$) obtained for continuous four-minute steady-state baseline and hypertensive challenge conditions. The grand mean of each of these parameter values based on all six animals is given (see Table 2). Before FPI, variation of both mean ΔPAR/ΔCPP and ΔmCVR/ΔCPP were positive during baseline and significantly increased during the challenge condition indicative of intact cerebrovascular regulation. For this condition both ΔrPBF/ΔCPP and ΔmCBF/ΔCPP remained relatively constant. After FPI, both mean ΔPAR/ΔCPP and ΔmCVR/ΔCPP were negative and decreased significantly during hypertensive challenge, while the changes of both ΔrPABP/ΔCPP and ΔmCBF/ΔCPP 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 CBF 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 PAR 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 PAR 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.

Table 1 Changes of mean (±SEM) ABP, ICP, CPP, mCVR, mCBF, PAD, PAR and rPABF in response to norepinephrine challenge before and following fluid percussion injury

	N	ABP (mmHg)	ICP mmHg	CPP (mmHg)	mCVR (mmHg/mL/min)	mCBF (mL/min)	PAD (μm)	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 (±0.07)‡	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 (±0.07)‡	78.6 (±0.7)‡	2.8 (±0.03)‡	26.5 (±0.2)‡	87.2 (±0.5)‡	94.3 (±1.9)‡	0.84 (±0.0003)‡

ABP, arterial blood pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; mCVR, model-derived assessments of cerebrovascular resistance; mCBF, model-derived assessments of cerebral blood flow; PAD, pial arteriolar diameter; PAR, pial arteriolar resistance; rPABF, relative pial arteriolar blood flow; SEM, standard error of mean; FPI, fluid percussion brain injury

*Degree of significance between baseline prior to FPI and baseline after FPI at $P < 0.001$

†Degree of significance between baseline prior to FPI and baseline after FPI at $P < 0.005$

‡Degree of significance between baseline and challenge mean values at $P < 0.001$

§Degree of significance between baseline and challenge mean values at $P < 0.005$

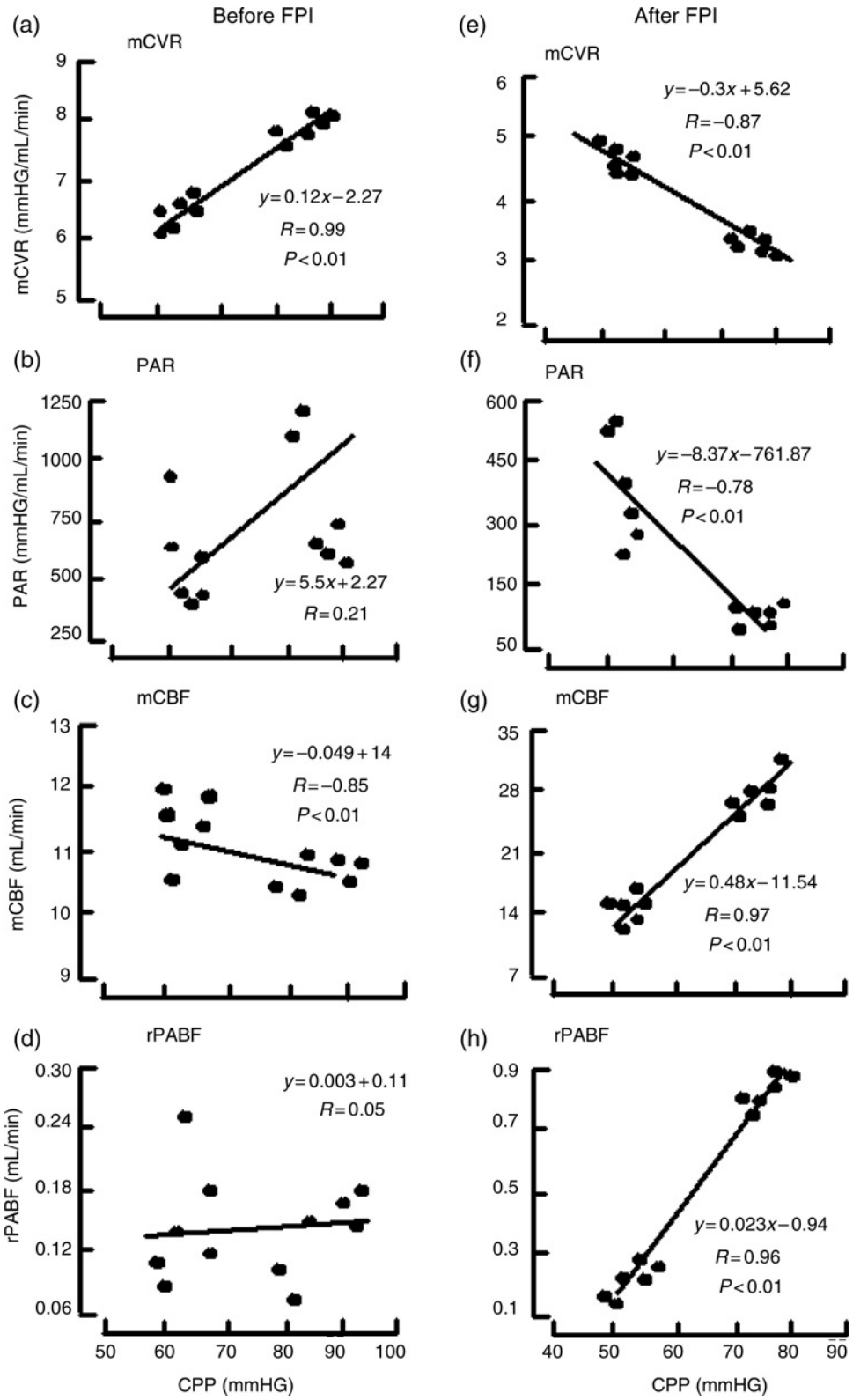

Figure 2 Grand mean parameters of mCVR, mCBF, PAR and rPABF with increased cerebral perfusion pressure induced by hypertensive challenge before and after fluid percussion injury. Before FPI: (a) mCVR and (b) PAR. Model-derived mCVR and PAR increased directly with increasing CPP. (c) mCBF and (d) rPABF. 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 grand mean values ($n = 12$). Value of SEM is within each symbol. mCVR, model-derived assessments of cerebrovascular resistance; mCBF, model-derived assessments of cerebral blood flow; PAR, pial arteriolar resistance; rPABF, relative pial arteriolar blood flow; CPP, cerebral perfusion pressure; FPI, fluid percussion brain injury; SEM, standard error of mean

Table 2 Grand mean (±SEM) regression line slopes of ΔPAR, ΔmCVR, ΔrPBF and ΔmCBF with respect to ΔCPP during steady-state baseline and hypertensive challenge conditions before and following FPI

	N	ΔPAR/ΔCPP (mmHg/mL/min/mmHg)	ΔmCVR/ΔCPP (mmHg/mL/min/mmHg)	ΔrPBF/ΔCPP (mL/min/mmHg)	ΔmCBF/ΔCPP (mL/min/mmHg)
Before FPI					
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)
After FPI					
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)*

mCVR, model-derived assessments of cerebrovascular resistance; mCBF, model-derived assessments of cerebral blood flow; PAR, pial arteriolar resistance; rPABF, relative pial arteriolar blood flow; FPI, fluid percussion brain injury; SEM, standard error of mean

*Degree of significance between baseline and challenge conditions at $P < 0.001$

†Degree of significance between baseline prior to FPI and baseline after FPI at $P < 0.001$

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, ΔmCVR/ΔCPP, 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 a 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 CBF were not done in this study, only assessment 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 estimates of regional PAR and blood flow and the corresponding model-derived global estimates of mCVR and mCBF with CPP during both intact and impaired cerebrovascular regulation. Because of the parallel vascular pathway structure of the brain, the reported regional estimates of pial arteriolar flow and resistance are several orders of magnitude different than the corresponding global estimates of CBF and resistance. The nature of the interconnection of the parallel vascular pathway structure may also be reflected in the pattern of relationships between the regional and computationally derived values of blood flow and vascular resistance, mCBF versus rPABF, PAR versus mCVR and PAR versus mCBF for the conditions of intact vascular tone before FPI and impaired vascular tone following FPI. These correlations were weak and non-significant, which may have been indicative of the conditions of heterogeneous blood flow and vascular pathway resistance that exist during intact vascular tone. In contrast, with loss of tone and pressure passive flow, these correlations were significant and robust, which may have been indicative of the conditions of homogenous changes in blood flow and vascular pathway resistance that occurred following severe FPI. Moreover during intact tone, changes in the overall flow through the parallel vascular pathways may reflect the observed increase above baseline values of both the regional regression line parameter, ΔPAR/ΔCPP, and global regression line parameter, ΔmCVR/ΔCPP, during hypertensive challenge. 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] Of note, the global model-derived values of blood flow and vascular resistance are data driven from pressure recordings. These pressure recordings define a specific dynamic relationship between ICP and ABP for a given brain size. At baseline for the group of uninjured piglets the 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/100 g/min with a cerebrovascular resistance of approximately 1.4 mmHg/mL/100 g/min. Studies using anesthetized newborn piglets reported control CBF values that ranged from 38 to 70 mL/100 g/min.[15–18] Further experiments designed to validate directly the accuracy of the parameter identification modeling method by directly comparing model-derived estimates with absolute measurements of CBF and CVR are needed.

Second, 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 the arterial–arteriolar bed,[17] the proposed methodology may be limited to brain injuries that involve generalized diffuse injury to the cerebral arteriolar vascular bed or least large proportions of the total cerebral vasculature. These methods would not detect effects of small focal injuries on localized loss of vascular control. However, in such cases, most of the cerebral vasculature would be well regulated and consistent with 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 CBF can be used to monitor the state of cerebrovascular regulation and cerebral perfusion. The ability to monitor continuously 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]

Author contributions: All authors participated in the design, interpretation of the studies and analysis of data and review of the manuscript. MLD and NN conducted the experiments and CWL was involved in experimental design and discussions of data interpretation and functional significance. MLD wrote the initial draft and NN and CWL provided input for modifications of that draft to accomplish the final manuscript.

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REFERENCES

1 Bullock MR, Povlishshock JT. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma* 2007;**24**:S59–64
2 Howells T, Elf K, Jones P, Ronne-Engstrom E, Piper I, Nilson P, Andrews P, Enbald P. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. *J Neurosurg* 2005;**102**:311–7
3 Constrant CF, Valadka AB, Gopinath SP, Hannay HJ, Robertson CS. Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. *J Neurosurg* 2001;**95**:560–8
4 Daley ML, Pourcyrous M, Timmons SD, Leffler CW. Assessment of cerebrovascular autoregulation: changes of highest modal frequency of cerebrovascular pressure transmission with cerebral perfusion pressure. *Stroke* 2004;**35**:1952–6
5 Narayanan N, Leffler CW, Daley ML. Influence of hypercapnic vasodilation on cerebrovascular autoregulation and pial arteriolar bed resistance in piglets. *J Appl Physiology* 2008;**105**:152–7
6 Narayanan N, Leffler CW, Daley ML. Assessment of cerebrovascular resistance with a model of cerebrovascular pressure transmission. *Med Eng Phys* 2009;**31**:254–60
7 Fung YC. *Biomechanics: Mechanical Properties of Living Tissues*. 2nd edn. Chapter 1. New York: Springer, 1993:11
8 Don DS, James F. Pressure in the pial arterial microcirculation of cat during changes in systemic arterial blood pressure. *Circ Res* 1972;**31**:229–39
9 Scot LH, Glenn BH, Michael JR. Arterial and microvascular contributions to cerebral cortical autoregulation in rats. *Am J Physiol* 1984;**15**:H17–24
10 Czosnyka M, Piechnik P, Richards HK, Kirpatrick P, Smielewski P, Pickard JD. Contribution of mathematical modeling to the interpretation of bedside tests of cerebrovascular autoregulation. *J Neurol Neurosurg Psychiatry* 1997;**63**:721–31
11 Ljung L. *System Identification Toolbox User's Guide*. Natick, MA: The MathWorks, 1991:8–9
12 Ramsay SC, Murphy K, Shea SA, Friston KJ, Lammertsma AA, Clark JC, Adams L, Guz A, Frackowiak RSJ. Changes in global cerebral blood flow in humans: effect on regional cerebral blood flow during a neural activation task. *J Physiol* 1993;**471**:521–34
13 Ursino M. A mathematical study of human intracranial hydrodynamics. Part I – The cerebrospinal fluid pulse pressure. *Ann Biomed Eng* 1988;**16**:379–401
14 Ursino M, Lezzi M, Stocchetti N. Intracranial pressure dynamics in patients with acute brain damage: a critical analysis with the aid of a mathematical model. *IEEE Trans Biomed Eng* 1995;**42**:529–40
15 Ferrara JJ, Dyess DL, Peeples GL, Christenberry DP, Roberts WS, Tacchi EJ, Swafford AN, Ardell JL, Powel RW. Effects of dopamine and dobutamine on regional blood flow distribution in the neonatal piglet. *Ann Surg* 1995;**221**:331–42
16 Baranov D, Armstead WM. Selective blockade of AT1 receptor attenuates impairment of hypotensive autoregulation and improves cerebral blood flow after brain injury in the newborn pig. *Anesthesiology* 2003;**99**:1118–24
17 Oden JP, Stiris T, Hansen TWR, Bratlid Dag. Cerebral blood flow during experimental hypoxaema and ischaemia in newborn piglet. *Acta Padiatr Scand Suppl* 1989;**360**:13–9
18 Bauer R, Walter B, Torossian A, Fritz H, Schlonski O, Jochum T, Hoyer D, Reinhart K, Zwiener U. A piglet model for evaluation of cerebral blood flow and brain oxidation metabolism during gradual cerebral perfusion pressure decrease. *J Pediatr Neurosurg* 1999;**30**:62–9
19 Shibata M, Einhaus S, Schweitzer JB, Zuckerman S, Leffler CW. Cerebral blood flow decreased by adrenergic stimulation of cerebral vessels in anesthetized newborn pigs with traumatic brain injury. *J Neurosurg* 1993;**79**:696–704

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