Assessment of Cerebrovascular Autoregulation
Changes of Highest Modal Frequency of Cerebrovascular Pressure Transmission With Cerebral Perfusion Pressure

Michael L. Daley, PhD; Massroor Pourcyrous, MD; Shelly D. Timmons, MD, PhD; Charles W. Leffler, PhD

**Background and Purpose**—Development of a method to continuously assess cerebrovascular autoregulation of patients with traumatic brain injury would facilitate therapeutic intervention and thus reduce secondary complications.

**Methods**—Changes in arterial blood pressure (ABP), intracranial pressure (ICP), cerebral blood flow velocity (CBFV), and pial arteriolar diameter (PAD) induced by acute pressor challenge (norepinephrine; 1 μg/[kg · min]) were evaluated in both uninjured and fluid percussion injured piglets equipped with cranial windows. The linear correlation coefficient and corresponding slope of the regression line of the relationship between highest modal frequency (HMF) of cerebrovascular pressure transmission of ABP to ICP and cerebral perfusion pressure (CPP) were determined for each challenge.

**Results**—For all uninjured piglets, pressor challenge resulted in an inverse relationship between HMF and CPP characterized by significant negative correlation values and negative corresponding regression line slopes with respective group mean values (±SD) of −0.50 (±0.14) and −0.6 (±0.44) Hz/mm Hg, respectively. Consistent with functional autoregulation of the uninjured preparations, pressor challenge resulted in a decrease of PAD, and CBFV remained relatively constant. For all injured piglets, pressor challenge resulted in direct relationship between HMF and CPP, characterized by positive correlation values and corresponding regression line slopes with group mean values of 0.48 (±0.21) and 1.13 (±2.08) Hz/mm Hg, respectively. Consistent with impaired autoregulation, PAD and CBFV increased during pressor challenge after brain injury.

**Conclusions**—Evaluation of changes of the HMF of cerebrovascular pressure transmission with respect to CPP changes permits continuous monitoring of cerebral autoregulation. (Stroke. 2004;35:1952-1956.)

**Key Words:** cerebrovascular disorder • intracranial pressure • brain injuries

A method is needed to continuously evaluate the state of autoregulation to help devise targeted therapies and reduce secondary complications for patients with severe head injury during intensive care management. For example, the cerebral perfusion pressure (CPP)-oriented therapeutic approach proposed by Rosner assumes that autoregulation is preserved to some degree after injury, and thus CPP can be maintained within the autoregulatory range by management. In particular, in the range of unimpaired autoregulation, the arterial–arteriolar bed actively adjusts the caliber of its vessels in response to changes in CPP to maintain a relatively constant cerebral blood flow by dilating when CPP decreases and constricting when CPP increases. When the cerebrovascular bed is dysfunctional, the caliber of each vessel within the arterial–arteriolar bed either passively follows CPP changes or tends to remain in a fixed state caused by either traumatic vasospasm or perhaps a quasi-equilibrium state between intravascular, myogenic, and extravascular forces that results in a balance between passive distension and passive compression of the vascular bed. Application of CPP-oriented therapy when autoregulation has been lost may result in an imbalance of Starling forces leading to increased net filtration and further brain injury by increased production of vasogenic edema.

Others have classified patients according to the frequency characteristics of cerebrovascular pressure transmission of arterial blood pressure (ABP) to intracranial pressure (ICP). We have shown recently that changes in high-frequency cerebrovascular transmission characteristics correspond to the change in state of dilation of the vascular bed. In this study, the high-frequency characteristics of cerebrovascular transmission are evaluated by the highest modal frequency (HMF), which is the highest vibrational mode by which energy is transferred from ABP to ICP. The purpose of this laboratory study was to examine the efficacy of a method to continuously assess the status of autoregulation by evaluating...
changes in the HMF in relation to changes in CPP induced by pressor challenge before and after fluid percussion brain injury.

**Materials and Methods**

**Laboratory Materials and Manipulations**

The protocol for this study was approved by the Animal Care and Use Committees of the University of Tennessee Health Science Center and the University of Memphis. The procedures used were similar to those described for other animal studies using this piglet model. Pitglets were purchased from commercial breeders in Mississippi by the Department of Comparative Medicine at the University of Tennessee Health Science Center. Initially, each animal was administered ketamine (33 mg/kg) and acepromazine (3 mg/kg) intramuscularly. 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) at a rate ranging between 8 and 24 breaths per minute with a pressure-limited pulse ventilation pattern. Periodic assessments of the partial pressure of carbon dioxide, oxygen, pH, and hemoglobin in arterial blood, as measured by Instrumentation Laboratory 1306, pH/Blood Gas Analyzer were determined and used to guide ventilation setting to maintain normal blood gas levels and pH at approximately 7.35, pCO2 between 42 and 45 mm Hg, and pO2 between 85 mm Hg, and 7.35, respectively. Hemoglobin remained relatively constant at 14.5 g/dL during each experiment. Anesthesia was maintained with chloralose (50 mg/kg IV initially, followed by 3 to 5 mg/kg hourly). Rectal temperature of animals was kept at 38°C to 39°C.

**Fluid Percussion Injury**

Our previously described fluid percussion apparatus was attached to a preimplanted cylindrical adapter mounted on the skull over the exposed dura of the right parietal cortex. The cylinder was filled with 0.9% saline and maintained airtight. Brain injury is caused by striking the piston with the pendulum. With a pressure sensor (Honeywell 236PC30GW) coupled to the apparatus tip, mean impact pressure values representing 8-second segments, the autoregressive dynamic model is defined by the HMF, and thus it was transferred from ABP to ICP. Mean impact pressure values representing 8-second segments, the autoregressive difference equation is defined by the HMF, and thus it was transferred from ABP to ICP.

**Challenge With Norepinephrine**

ABP elevation was accomplished by infusing norepinephrine (1 μg/[kg·min]) into the femoral vein during a 5-minute period. Time of the hemodynamic parameters was determined with the administration of norepinephrine and ranged from 17 to 93 minutes postinjury with a mean (±SD) of 39.3 (±27.2) minutes.

**Placement of Cranial Window**

A cranial window 2 cm in diameter was placed over the left parietal cortex and secured with dental acrylic. The space under the window was filled with artificial cerebrospinal fluid (150 milliequivalent [meq] Na+/L, 3 meq K+/L, 2.5 meq Ca2+/L, 1.2 meq Mg2+/L, 132 meq Cl−/L, 3.7 mmol/L glucose, 6 mmol/L urea, and 25 meq HCO3−/L with pH at 7.33, pco2 42 to 45 mm Hg, and pO2 between 43 and 50 mm Hg) through the stainless steel injection ports incorporated into the sides of the window.

**Pial Arteriolar Diameter Measurement**

In each piglet, taped VHS recordings of 3 pial arterioles at 3600 frames/sec were used to compute the mean diameter for every 8 seconds as described previously. Mean value of each pial arteriolar diameter (PAD) was computed from 10 consecutive measurements at baseline and challenge. For each set of 3 arteriolar diameter measures, 1 grand mean PAD was determined for each condition.

**Cerebral Blood Flow Velocity**

A PeriFlux 4001 laser Doppler flow meter (Perimed AB) was used to measure changes of cerebral blood flow velocity (CBFV) in cortical tissue contralateral to the site of fluid percussion injury (FPI). The probe was removed during the percussive impact. The unit of velocity cannot be given a physiological definition and reflects a net particle flow within a 1-mm3 cube at the sensor tip. These values are not absolute and must be compared with one another.

**Data Acquisition**

Intraparenchymal ICP recordings obtained with a direct pressure monitor (Camino Laboratories) and femoral ABP recordings obtained with a SpaceLabs model 90623A monitor (SpaceLabs Inc) were digitized at 250 Hz with a system described previously. CPP was computed as the difference between ABP and ICP.

**Numerical Methods**

The third-order electrical analog circuit model proposed by Czosnyka et al defines the dynamic relationship of cerebrovascular pressure transmission by a differential equation of the structure described as:

\[ d^3Y/dt^3 + a_1 d^2Y/dt^2 + a_2 dY/dt + a_0 Y(t) = b_1 U(t) + b_2 dU/dt + b_3 d^2U/dt^2 \]

Modal analysis is the procedure of determining the principal modes by which energy is transferred in a linear system and specifying dynamic characteristics of a structure, namely the resonant frequencies and damping values. The high frequencies of cerebrovascular pressure transmission are reduced by vasodilation. The highest vibration mode by which energy is transferred from ABP to ICP is defined by the HMF, and it was selected to assess the dilation state of the cerebrovascular bed. The radian modal frequencies of cerebrovascular pressure transmission characterized by equation 1 above are defined by the roots of the polynomial equation:

\[ \lambda^3 + a_1 \lambda^2 + a_2 \lambda + a_0 = 0 \]

The numerical procedures used to obtain the cerebrovascular pressure transmission HMF are given in a flowchart (Figure 1). In the initial numerical steps of our analysis procedure, the digitized pressure recordings are used to define the constant parameters of the difference equation described as:

\[ Y[(n+3)T] + a_1 Y[(n+2)T] + a_2 Y[(n+1)T] + a_0 Y(nT) = b_1 U(nT) + b_2 dU(nT) + b_3 d^2U(nT) \]

This equation is a difference equation approximation of the continuous differential equation description of cerebrovascular pressure transmission given in equation 1. For each 2000 paired samples of pressure values representing 8-second segments, the autoregressive moving average (ARMAX) numerical technique was applied using MATLAB System Identification Toolbox software (Mathworks) to obtain the minimum least square error set of constants a0, a1, a2, and b1, b2, b3. Using MATLAB Control Systems Toolbox software, the constants of the continuous description given in equation 1 are determined. With these constants, the modal frequencies of the dynamic system described by equation 1 are determined by the solution of the polynomial equation given in equation 2. Grand mean HMF values for baseline and challenge conditions were calculated from 10 consecutive HMF values obtained during each condition.

**Statistical Methods**

All mean values are reported with ±SD values. In all cases, the degree of significance between 2 mean values was determined by using the t statistic.

**Results**

Fluid percussion injury resulted in a decrease of mean baseline value of CPP (P<0.05), whereas mean baseline values of ABP, HMF, ICP, and PAD did not change significantly (Table). Because of brain movement resulting from...
the percussive impact, replacement of the CBFV probe after impact likely resulted in interrogation of different cortical tissue. Thus, comparisons of CBFV values before and after FPI are not valid.

Before brain injury, pressor challenge by intravenous administration of norepinephrine at 1 μg/(kg.min) during a 5-minute period caused a significant increase \( (P<0.05) \) in both grand mean ABP and grand mean CPP by more than 25 mm Hg (Table). Grand mean ICP also increased. For the individual preparations, 3 piglets demonstrated significant increases in mean ICP and 1 piglet demonstrated a decrease in mean ICP. As a group, both mean \%ΔPAD \( (±SD) \) and mean \%ΔCBFV \( (±SD) \) decreased slightly by -1.5\% \( (±5.1\%) \) and -3.6\% \( (±12.0\%) \), respectively. The PAD decrease translates to a 12.2\% increase in resistance. Furthermore, mean HMF decreased during the challenge, and group means \( (±SD) \) of correlation values and slope values of the regression line of the relationship between ABP and ICP were determined as -0.50 \( (±0.14) \) and -0.60 \( (±0.44) \) Hz/mm Hg, respectively.

After induction of brain injury, challenge with norepinephrine caused a significant increase \( (P<0.05) \) in ABP, which was accompanied by an increase of CPP of 25 mm Hg (Table). Grand mean ICP increased from 6.4 mm Hg to 9.2 mm Hg, with 4 challenges producing a significant increase of mean ICP. Both mean \%ΔPAD \( (±SD) \) and mean \%ΔCBFV \( (±SD) \) increased by 12.2 \( (±8.3\%) \) and 8.47 \( (±20.0\%) \), respectively (Table). The observed significant increase in the grand mean of PAD from 76.8 to 86.0 μm

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**Mean \( (±SD) \) ABP, ICP, CPP, HMF, PAD, and Relative CBFV Before and After Challenge With Norepinephrine**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>ABP (mm Hg)</th>
<th>ICP (mm Hg)</th>
<th>CPP (mm Hg)</th>
<th>HMF (Hz)</th>
<th>PAD (μm)</th>
<th>CBFV (VU)*</th>
<th>%Δ in PAD</th>
<th>%Δ in ABP</th>
<th>%Δ in ICP</th>
<th>%Δ in CBFV</th>
<th>R†</th>
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<tr>
<td>Before FPI</td>
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<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>6</td>
<td>66.4 (±9.8)§</td>
<td>2.8 (±1.3)</td>
<td>66.3 (±11.2)†</td>
<td>47.0 (±22.1)</td>
<td>77.8 (±16.5)</td>
<td>130.6 (±77.7)</td>
<td>-1.5 (±5.1)§</td>
<td>43 (±24)</td>
<td>61 (±32)</td>
<td>-3.64 (±12)</td>
<td>-0.5 (±0.14)¶</td>
</tr>
<tr>
<td>Challenge</td>
<td>6</td>
<td>95 (±28.2)†</td>
<td>4.5 (±1.8)</td>
<td>91.7 (±28.6)†</td>
<td>40.1 (±14.7)</td>
<td>75.6 (±15.2)</td>
<td>126 (±85.4)</td>
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<tr>
<td>After FPI</td>
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<tr>
<td>Baseline</td>
<td>6</td>
<td>52.9 (±15.4)‡</td>
<td>6.4 (±6.9)</td>
<td>46.4 (±21.7)</td>
<td>32.4 (±5.7)§</td>
<td>76.8 (±5.8)§</td>
<td>124.9 (±118)</td>
<td>12.2 (±8.3)§</td>
<td>58 (±26)</td>
<td>44 (±28)</td>
<td>8.47 (±20)</td>
<td>0.48 (±0.21)¶</td>
</tr>
<tr>
<td>Challenge</td>
<td>6</td>
<td>84.1 (±28.6)‡</td>
<td>9.2 (±11.5)</td>
<td>75.1 (±37.2)</td>
<td>49.7 (±9.6)§</td>
<td>86.0 (±8.3)§</td>
<td>138 (±115)</td>
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All values represent mean \( (±SD) \).

*Unit of velocity (VU) indicates net particle velocity within 1 mm³ at tip of sensor.
†Correlation values based on 20 paired values of HMF and CPP.
§Denotes difference in mean values at \( P<0.05 \).
¶Denotes difference in mean values at \( P<0.01 \).
†Denotes difference in mean values at \( P<0.005 \).
A piglet model of pediatric traumatic brain injury and a P (0.005), and HMF directly correlated with CPP with a /H11021 grand mean HMF increased significantly after brain injury reflects a 36.4% decrease in vascular resistance. In addition, R/FPI. Consistent with passive vasodilation, challenge with norepinephrine resulted in a response consistent with active vasoconstriction in that a negative correlation value (R=-0.77) and negative slope (m) of the regression line (m=-0.317 Hz/mm Hg) between HMF and CPP were demonstrated, b. After FPI. Consistent with passive vasodilation, challenge with norepinephrine resulted in positive correlation values (R=0.34) and slope of regression line (m=0.325 Hz/mm Hg).

reflects a 36.4% decrease in vascular resistance. In addition, grand mean HMF increased significantly after brain injury (P<0.005), and HMF directly correlated with CPP with a mean R value (±SD) and slope of regression line (±SD) of 0.48 (±0.21) and 1.13 (±2.08) Hz/mm Hg, respectively.

An example from 1 piglet of the relationships of HMF and CPP during norepinephrine challenge before and after FPI is given in Figure 2. Before brain injury, all animals demonstrated a significant negative correlation between HMF and CPP. After induction of brain injury, all correlation values between HMF and CPP were positive. Before injury, the grand mean (±SD) values of correlation and slope of the regression line were −0.5 (±0.14) and −0.60 Hz/mm Hg, respectively, and after injury, these values were 0.48 (±0.21) and 1.13 (±2.1) Hz/mm Hg, respectively. The degree of significance of these grand mean values is P<0.005 and P<0.05 for the grand mean of correlation and the grand mean of the slope of the regression line, respectively.

Discussion
A piglet model of pediatric traumatic brain injury and a novel method to characterize changes in the cerebrovascular pressure transmission of ABP to ICP during pressor challenge were examined as a means to continuously assess the state of cerebrovascular autoregulation. Before injury, PAD decreased during pressor challenge consistent with active regulation and increased vascular tone. Average vascular resistance increased by 12.2%, producing increased dampening of the hemodynamic response with increasing CPP. This caused a decrease in the cerebrovascular pressure transmission HMF. The required graded increase of vascular resistance with increasing CPP to maintain relatively constant flow during active regulation is reflected in the observed significant negative correlation between HMF and CPP of cerebrovascular pressure transmission demonstrated by all uninjured animals. In contrast, pressor challenge after head injury resulted in an increase in PAD and CBFV, reflecting passive vasodilation, and an increase in CPP. Average vascular resistance decreased by 36.4%, causing reduced dampening of the hemodynamic response with increasing CPP, resulting in a significant (P<0.005) increase in HMF. Consistent with the graded nature of passive vasodilation with increasing CPP was the positive correlation between HMF and CPP demonstrated by all brain-injured animals in response to the pressor challenge.

Our findings provide the basis for further development of a method to continuously assess autoregulation in the intensive care setting by evaluating the relationship between changes in the HMF of cerebrovascular pressure transmission and CPP. The test criterion for loss of autoregulation can be defined as a positive significant correlation between HMF and CPP. Using this criterion, our findings of significant negative correlation between HMF and CPP in all animals from the pressor challenge before FPI demonstrate that the method has 100% specificity. After injury, all animals demonstrated a positive correlation between the HMF of cerebrovascular pressure transmission and CPP; but 2 correlation values were not significant. Such a result indicates that the method has a sensitivity of 66.7% for detecting loss of autoregulation.

Application of CPP-oriented therapy has potential risks for patients with impaired autoregulation. Artificial ABP elevation by administration of pressor agents can lead to elevation of ICP, increased capillary fluid filtration, and diminished fluid absorption caused by hydrostatic/oncotic pressure balance alteration. Because of these risks, clinical studies have explored the possibility of using ICP changes induced during pressor challenge as a method to assess autoregulation in patients with traumatic brain injury. Oertel et al evaluated hypertension tests in 23 patients with traumatic brain injury and found that the majority of the patients (61.7%) demonstrated an increase in ICP, suggesting impaired autoregulation.10 In a recent similar clinical study, Lang and Chesnut11 defined the following 3 types of ICP patterns induced by artificial elevation of ABP: (1) type 1 denoting an increase of ICP and passive regulation; (2) type 2 denoting no change in ICP and active regulation; and (3) type 3 denoting a decrease in ICP and active regulation. The authors reported that during the course of artificial ABP elevation, the pattern of a response sometimes changed, suggesting the transition through a “breakpoint,” either from passive to active or active to passive regulation.11 Our findings show that 3 similar patterns of HMF result from artificial ABP elevation. During active regulation, HMF is related inversely to ICP, a type 3 pattern. After FPI, 4 animals demonstrated the type 1 pattern, and 2 animals exhibited the type 2 pattern. The latter pattern may reflect a state in which the myogenic structural characteristics of vascular walls within the arterial–arteriolar bed prevent passive distension during pressor challenge. Comparisons of these reported clinical findings with our laboratory results must be considered in view of the following limitations. We placed the piglet’s head above the trunk; as a result, outflow of cerebrospinal fluid from cranial space to the spinal canal was likely enhanced. Thus, IPP was low, and intracranial compliance remained high before and after fluid percussion injury. In addition, our PAD measures may not reflect changes in the deeper arterioles within the brain. Nevertheless, during pressor challenge after induced brain injury, the majority of piglets demonstrated a significant increase in
mean ICP, and all piglets demonstrated a positive correlation between HMF and ICP.

Possible limitations of the proposed methodology and interpretation of our results should be noted. First, the methodology is limited in circumstances in which the regional sensitivity of the ICP monitor is reduced as result of the nature of the injury. Also, impairment in either small or remote focal regions that do not alter the pulsatility of the ICP recording would probably not be detected by this method. Second, the proposed methodology is designed to assess alterations in pressure regulation attributable to injury to the cerebrovascular bed. Average decrease in CPP after injury was ≈20 mm Hg. As a result, it is possible that the loss of pressure regulation after injury resulted from reduction in CPP below the normal physiological lower limit of pressure regulation and not because of vascular bed injury. However, these are newborn piglets, and the physiological lower limit for normal pressure regulation is much lower than that for more mature animals. Previously, we found that the lower limit pressure regulation for newborn pigs undergoing asphyxic challenge is in the region of 25 to 35 mm Hg. Moreover, there is no difference between the mean value of correlation (±SD) of HMF and CPP for the 2 injured piglets 0.56 (±0.37) with a mean baseline CPP before pressor challenge than the observed mean value of correlation (±SD) of 0.45 (±0.16) for the 4 injured piglets with a lower mean baseline CPP before pressor challenge.

The findings of this study indicate that relating changes of HMF to changes of CPP may be of even greater value for evaluating the state of cerebrovascular regulation than evaluating changes in mean ICP induced by pressor challenge alone. However, the conclusions of this study are only known to be applicable to a hypertensive challenge with norepinephrine under conditions of FPI obtained from an animal model with characteristics of diffuse axonal injury, and it might not apply to other situations or pathologies.6

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References
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