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## Variation in Cerebral Blood Flow Velocity with Cerebral Perfusion Pressure > 40 mm Hg in 42 Children with Severe Traumatic Brain Injury

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### Abstract

**Objective**—There is no information regarding the relationship between middle cerebral artery flow velocity (Vmca) and cerebral perfusion pressure in pediatric traumatic brain injury (TBI). We determined the incidence of low, normal and high mean Vmca when CPP is > 40 mm Hg in children with severe TBI.

**Design**—Prospective observational study

**Setting**—Level 1 pediatric trauma center

**Patients**—42 children < 17 years of age with an admission diagnosis of severe TBI (admission Glasgow Coma Scale [GCS] score < 9), TBI on computed tomography (CT) scan, tracheal intubation/mechanical ventilation and intracranial pressure (ICP) monitoring.

**Interventions**—None.

**Measurements and Main Results**—Bilateral middle cerebral arteries were insonated using transcranial Doppler ultrasonography (TCD) to calculate mean Vmca after TBI. Low mean Vmca was defined as Vmca < 2SD and high was defined as mean Vmca > 2SD. Patients were grouped by age (0.8–2.9, 3–5.9, 6–9.9, and 10–16.9 years) and gender to examine the relationship between CPP and low, high or normal mean Vmca. Potential confounders of the relationship between CPP and mean Vmca (ICP, PaCO<sub>2</sub>, hematocrit [Hct], sedation, fever and impaired autoregulation) were examined. Most (33; 79%) children had normal mean Vmca but 4 (9%) patients had low mean Vmca and 5 children (12%) had high mean Vmca despite CPP > 40 mm Hg. There was no difference in potential confounders of the relationship between CPP and mean Vmca except for Hct, which was lower (25 ± 4 [range 21–30]) in children with high mean Vmca. An inverse relationship between mean Vmca and Hct was also found in boys 10–16.9 years.

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**Conclusions**—Both low and/or high mean Vmca occur with CPP > 40 mm Hg in severe pediatric TBI. Of the potential confounders considered, only lower Hct was associated with high mean Vmca.

### Keywords

cerebral blood flow velocity; cerebral perfusion pressure; pediatric trauma; brain injury; blood pressure; middle cerebral artery flow

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### Introduction

Traumatic brain injury (TBI) is the leading injury in pediatric trauma [1] and a leading cause of morbidity and mortality in children over 1 year of age [2]. Following TBI, secondary insults such as hypotension [3], worsen outcome. Consequently, current guidelines suggest maintaining 1) systolic blood pressure > 5<sup>th</sup> percentile for age and 2) cerebral perfusion pressure (CPP) > 40 mm Hg after severe TBI [4]. Yet, it is unclear whether achieving these SBP and or CPP thresholds are associated with optimal and adequate cerebral blood flow (CBF).

One important mechanism by which hypotension or even “normotension” might result in cerebral hypoperfusion is via derangement in the normal cerebral autoregulatory process which normally maintains CBF relatively constant between a range of blood pressures [5]. Cerebral hypoperfusion (CBF < 25ml/100gm/min) is the dominant derangement in pediatric TBI and is associated with cerebral ischemia and poor outcome [6]. Early hypotension, especially occurring during the first 6 h after injury, is associated with poor outcome in pediatric TBI [7,8]. According to Hackbarth et al and others, the ability to maintain a CPP of  $\geq 50$  mm Hg was the single most important predictor of survival following pediatric TBI [9,10,11].

In 2003, the Pediatric Guidelines recommended that CPP < 40 mm Hg be avoided after severe TBI to prevent cerebral hypoperfusion and poor outcomes [4]. Although the guidelines suggest a CPP between 40 and 65 mm Hg likely represents an age-related continuum, there are no data documenting the relationship between CPP and CBF or that CPP > 40mmHg is associated with age-appropriate CBF. The paucity of such CBF data may be due to the fact that direct measurements of CBF using computed tomography based imaging in children with TBI pose certain challenges such as radiation risks. For these reasons, the use of transcranial Doppler (TCD) ultrasonography is appealing; this technology measures cerebral blood flow velocity (CBFV), which estimates CBF and correlates well with CBF because velocity of flow is proportional to the volume of flow through the vessels examined [12,13,14].

In this study, we hypothesized that maintaining CPP > 40 mm Hg is variably associated with normal mean velocity of the middle cerebral artery (Vmca), and therefore, aimed to determine the incidence of low and high mean Vmca when CPP is > 40 mmHg in children with severe TBI.

### Materials and Methods

After Institutional Review Board approval from the University of Washington (Seattle, Washington), we prospectively examined CPP and Vmca in children with severe TBI at Harborview Medical Center (Level 1 pediatric trauma center). Consent was obtained from parents or legal guardians.

### Study Participants

Children age < 17 years admitted to the Harborview Medical Center pediatric intensive care unit (PICU) with an admission diagnosis of severe TBI (Glasgow Coma Scale [GCS] score < 9), TBI on computed tomography (CT) scan, tracheal intubation/mechanical ventilation and

intracranial pressure (ICP) monitoring were considered eligible. Children with extracranial injuries were also included. Patients with hemodynamic instability (per treating intensivist if significant hypotension or hypertension was present immediately before testing) or no available parent/guardian were excluded. We reviewed medical records for eligibility, relevant medical history, and physiologic data.

### Measuring Middle Cerebral Artery Blood Flow Velocity

Following admission to the PICU, a single measure of each (right and left)  $V_{mca}$  were obtained within 0 to 72 hours by TCD ultrasonography (Multidop X;DWL. Corp., Sipplingen, Germany) with a 2-MHz ultrasound probe [15], at patient bedside. Previously described age-appropriate depths were referenced and used to insonate the middle cerebral artery [16]. A registered vascular technologist, with more than 10 years of experience using TCD ultrasonography, insonated the middle cerebral arteries. Bilateral middle cerebral artery flow velocities ( $V_{mca}$ ) were averaged and the mean  $V_{mca}$  was used in the analysis.

### Cerebral Hemodynamic Data

Recorded blood pressures were non-invasive (cuff) measurements and intraarterial catheter measurements in PICU. When both non-invasive and invasive blood pressure readings were available, we used the invasive measurements. Each available CPP, PaCO<sub>2</sub>, and ICP at the time of measuring  $V_{mca}$ , were abstracted and entered into Excel and SPSS datasheets. Mean  $V_{mca}$  values were compared to previously published  $V_{mca}$  data, which are normed for age and gender [16,17,18]. Information regarding hematocrit (Hct), temperature, and the use of sedation were recorded. When cerebral autoregulation testing was performed, these data were recorded and are included in the analysis. Autoregulatory status was determined using the commonly used and published Autoregulatory Index (ARI) which examines estimated cerebrovascular resistance (eCVR) and MAP [15];  $ARI = \% \Delta eCVR / \% \Delta MAP$ ; autoregulation was considered intact if the ARI was  $\geq 0.4$ .

### Statistical Analysis

Descriptive statistics were used to present clinical characteristics. We first examined the difference between the means of right and left  $V_{mca}$  using paired T-tests. Since no difference was found in  $V_{mca}$  between the two sides, we used mean  $V_{mca}$  in the analysis to examine the relationship between CPP and mean  $V_{mca}$ . Each mean  $V_{mca}$  was defined as low ( $< 2SD$ ), normal or high ( $> 2SD$ ) by age and gender according to previously published age and gender  $V_{mca}$  norms [16,17,18].

Patients were first divided into 4 age groups (0.8–2.9, 3–5.9, 6–9.9, and 10–16.9 years) based on previously published data [16,17,18] and then each age group was divided by gender, for a total of 8 categories of description for CPP and mean  $V_{mca}$ . The relationship between CPP and mean  $V_{mca}$  was examined separately by age and gender. With the exception of the group of 10–16.9 year old boys which are formally analyzed, the raw data are described without formal analysis (small sample group size) using scatter plots. These results are displayed via scatter plots. For the largest sample size (boys 10–16.9 years of age) relationships between mean  $V_{mca}$  and CPP, PaCO<sub>2</sub>, ICP, Hct and Temp were examined using Spearman's rank correlation. For the 0.8–2.9 and 6–9.9 age groups, there are no gender norms, hence we examined data for these subjects by age only.

Student's T tests of unequal variance were used to analyze differences in the variables that potentially confound the relationship between CPP and mean  $V_{mca}$  such as ICP, PaCO<sub>2</sub> and hematocrit (Hct); these results are presented separately for patients with low, high, and normal mean  $V_{mca}$ . The relationship between the number of patients who had low PaCO<sub>2</sub> ( $< 35$  mm Hg), high ICP ( $> 20$  mm Hg), fever (temperature  $> 38.5^{\circ}$  C), sedation and impaired

autoregulation (when data available) in low and high mean Vmca groups was examined using Fisher's exact or  $\chi^2$  test, as appropriate.

SPSS version 11.5 (SPSS Inc., Chicago, IL) was used for data entry and analysis. Data are presented as mean  $\pm$  SD, or n (%).  $p < 0.05$  was considered significant.

## Results

### Demographic and Baseline Clinical Characteristics (Table 1)

Forty-four children were enrolled and underwent TCD ultrasonography. Two children were excluded because PaCO<sub>2</sub> data were out of acceptable range in the PICU, thereby leaving data from 42 children for analysis. Children were  $8.9 \pm 5.2$  (0.8–16.0) years (Table 1). Most (71%) were male. Motor vehicle crash (26%) and falls (26%) accounted for the majority of injuries. Most patients had extracranial injuries, including 7 who had pulmonary injury (contusion or pneumothorax). Three children had inflicted trauma (7%). All patients received a head computed tomography scan in the emergency department. The exact time of TCD ultrasonography testing was recorded in 32 (76%) patients; in these patients, the median time of testing was  $36 \pm \text{SEM } 3.0$  hours). During study testing, sedation with either propofol or midazolam/fentanyl was used in 27 (81%) patients; barbiturates were not used. Cerebral autoregulation measurements were available in only 27 (64%) patients. The average GCS was  $4 \pm 1.2$  (3–7) on PICU admission. Two (4%) children died in hospital prior to discharge.

### Incidence of low, normal and high mean Vmca

All 42 children had CPP  $> 40$  mm Hg (42–87 mm Hg) at time of TCD ultrasonography. Table 2A presents the incidence of low, high and normal mean Vmca; most (33; 79%) children had normal mean Vmca but 4 (9%) patients had low mean Vmca and 5 children (12%) had high mean Vmca despite CPP  $> 40$  mm Hg.

### Relationship between CPP and mean Vmca

There was no obvious relationship between CPP and mean Vmca within the age and gender groups examined, including the group with the largest sample size (N=20) of boys 10–16.9 years old (Spearman's  $\rho = -0.05$ ;  $p = 0.84$ ; Figure 1A).

### Factors associated with low and high mean Vmca (N=42)

At the time of TCD ultrasonography, PaCO<sub>2</sub> for the entire cohort was  $35 \pm 3$  (30–42) mm Hg, ICP was  $15 \pm 7$  (4–28) mm Hg and Hct was  $30 \pm 4\%$  (23–37). There were also no differences in PaCO<sub>2</sub>, ICP or Hct between patients with low mean Vmca vs. normal mean Vmca (Table 2A). However, Hct was lower ( $25 \pm 4$  [range 21–30]) in children with high versus normal mean Vmca groups ( $p = 0.02$ ; Table 2A). There was no relationship between number of patients with low PaCO<sub>2</sub>, high ICP, or number of patients with fever, sedation or impaired autoregulation in the high and low mean Vmca groups when compared to the normal mean Vmca group (Table 2B).

### Mean Vmca and confounder data in boys 10–16.9 years old (N=20)

In the range of CPP examined, the majority (18; 90%) had normal mean Vmca. Two (10%) patients had high Vmca. There was a negative correlation between Hct and mean Vmca (Spearman's  $\rho = -0.52$ ;  $p = 0.02$ ) but no relationship between mean Vmca and PaCO<sub>2</sub>, ICP and temperature (Figure 2A–D). Cerebral autoregulation was examined in all of these patients; it was intact in 15 (75%) and impaired in 5 (25%).

### Data from 9 children with low or high mean Vmca (N=42)

Of the 9 patients whose mean Vmca fell out of range for age and gender, 5 had high (>2 SD) and 4 had low (<2 SD) mean Vmca in 5 boys and 4 girls. There was a non-significant relationship between high Vmca and fever and low Vmca with impaired cerebral autoregulation (Table 2A–B)

### Discussion

There are currently no data examining the relationship between CPP and CBF in severe pediatric TBI. The main finding of this study is that mean Vmca can be low, high or normal for age and gender despite CPP > 40 mm Hg. We also found that patients with high mean Vmca had lower Hct than patients with normal mean Vmca. Since this study is not powered to formally examine relationships between Vmca and the variables examined, we cannot definitively conclude that high mean Vmca is not associated with PaCO<sub>2</sub>, high ICP, fever or sedation; however, we did not observe such an association.

In healthy children, CBF is highest during early childhood [19], and gender differences in mean Vmca and Vbas (basilar) are observed prior to puberty [17,18]. Healthy girls between ages 4–16 have higher mean Vmca than do age-matched boys. Children with TBI have lower mean Vmca than children without TBI [20]. These differences in age and gender biology make it important in order to determine the association between blood pressure and mean Vmca by age and gender. Historically, CBF < 20 ml/100g/min signified hypoperfusion, and neuronal death occurs when CBF is 10–15 ml/100g/min. Although cerebral hypoperfusion is associated with cerebral ischemia and poor outcome after TBI [21], high CBF is also problematic and can lead to hyperemia, increased ICP and poor outcome [19,20]. In either case, we assume that CBF is involved in the casual pathway between CPP and outcome. Consistent with the 2003 Pediatric Guidelines, we chose CPP > 40 mm Hg as a threshold blood pressure because outcomes are better when CPP exceeds 40 mm Hg [4]. The relatively high incidence of both low and high mean Vmca during “normotension” are similar to previously published data in adult TBI [22,23]. We examined the relationship between CPP and mean Vmca for each group to explore the presence of a threshold CPP by age but there was no such pattern. The fact that there was no obvious relationship between Vmca and CPP and that most Vmca values were normal for age and gender is generally consistent with the 2003 Pediatric Guidelines. However, the variability in mean Vmca, despite categories of what clinicians would consider acceptable CPP, argues for both individual and advanced neuromonitoring in pediatric TBI.

In this study, we explored some potential causes of low and high mean Vmca even when CPP was > 40 mm Hg. In this small sample, low mean Vmca was not associated with hypocarbia, sedation or high ICP. None of the subjects were treated with hypothermia or barbiturates and we did not have data on cerebral metabolic rate of oxygen (CMRO<sub>2</sub>), thus cannot comment on whether low CMRO<sub>2</sub> led to low mean Vmca. However, since flow–metabolism coupling is typically intact even in severe TBI, the observed low mean Vmca may be in response to changes in CMRO<sub>2</sub>. While our patients had CPP > 40 mm Hg, we cannot be certain that mean Vmca was low because the lower limit of autoregulation (LLA) exceeded the CPP 40 mm Hg threshold. In fact, the LLA in pediatric TBI is not known and may vary considerably given the heterogeneous nature of TBI. In this study, high mean Vmca was associated with low Hct. The relationship between Hct and mean Vmca is well described; the rheological properties of anemia result in vasodilation and increased CBF [24]. However, there is little information regarding optimal Hct in pediatric TBI [25]. Finally, impaired cerebral autoregulation could lead to either cerebral hypoperfusion or hyperemia.

Although we used mean Vmca to describe cerebral hemodynamics other measures have also been used in previous studies. Low diastolic velocities (Vd) and high pulsatility indices (PI)

have been shown to be associated with poor outcome in children and adults with TBI [26,27, 28]. Despite the correlations between PI and CPP [29,30] and the fact that measuring PI is independent of insonation angle, we used mean Vmca as our measure primarily because of existing data on age and gender norms for Vmca. We wanted to consider these developmental differences in our analysis of the relationship between CPP and Vmca.

This study has some limitations. First, given the small numbers of patients in each age/gender group, this study is largely descriptive. The number of subjects was too small to allow formal examination of CPP and mean Vmca by age and gender for each group and this study is not powered to state conclusions regarding relationships between Vmca and the variables examined in Tables 2a and 2B, including ICP and PaCO<sub>2</sub>. Our findings may not be generalized to children less than 4 years or between 8 and 10 years because of the small size in these groups. However, we thought it important to describe the data from younger children since young children have the worse outcome after TBI. While, we could not determine the correlation between CPP and mean Vmca within each group, data from this study (specifically the variability data) will allow for formal power calculations needed to better examine the relationship between CPP and mean Vmca for each age and gender group. Also due to the small sample size, we could not examine all potential confounders. We chose to examine the most potent determinants of Vmca such as ICP, Hct, and PaCO<sub>2</sub> but were not powered to test for different levels (doses, duration, types) of sedation or temperature (intensity, duration) and therefore grouped patients into broader categories to provide preliminary examination of these potential confounders. Also, CBF and or CBFV may represent the underlying pathophysiology and as such may differ despite similar clinical neurological scores, such as the GCS. However, the number of patients with each distinguishing pathophysiology is quite small. Additionally, as autoregulation testing was not done in all patients and not all patients had time of testing recorded, we only presented groups that had available data. Similarly, we were not able to determine the incidence of cerebral ischemia, not all patients had autoregulation testing and we do not have CMRO<sub>2</sub> data. This is important because low CBF may not be problematic following TBI if CMRO<sub>2</sub> is low and there is a compensatory increase in oxygen extraction fraction [31]. We did not consider ventilator pressures or pulmonary compliance as potential confounders of Vmca. Finally, we do not have direct measures of CBF. The lack of relationship between fever and high Vmca and impaired autoregulation with low Vmca is likely due to the small number of patients. Although a standard tool for use in complications of sickle cell disease [32] and cerebral vasospasm following subarachnoid hemorrhage [33], it is largely a research tool in TBI [34]. While we cannot advocate the use of TCD ultrasonography in pediatric TBI, the absence of other feasible determinants of CBF in these patients renders it a potentially useful [14], noninvasive tool for use at the bedside. Despite these limitations, however, these new data provide new insight into the variation in mean Vmca, and possibly CBF, with regard to current recommendations of adequate CPP. Furthermore, we speculate the use of advanced neuromonitoring, which may include TCD, may guide CPP management in the future.

In summary, this is the first study to document the variation in mean Vmca following pediatric TBI when CPP is greater than 40 mm Hg. Both low and high mean Vmca were observed with what is currently considered acceptable blood pressure in severe pediatric TBI. Advanced neuromonitoring is needed to better understand whether the variability in mean Vmca reflects the variability in CMRO<sub>2</sub> and whether empiric CPP management is appropriate in severe pediatric TBI.

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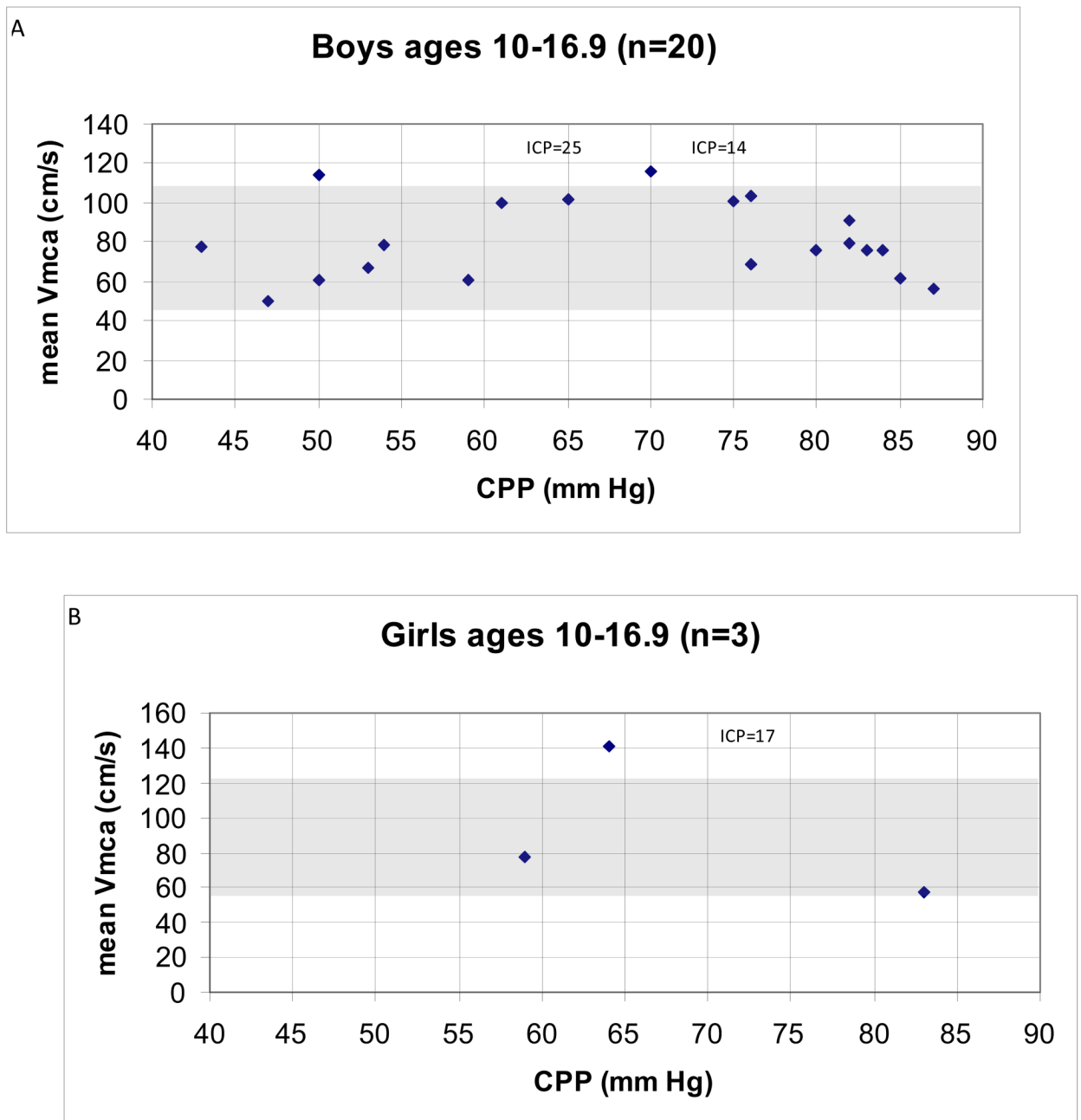
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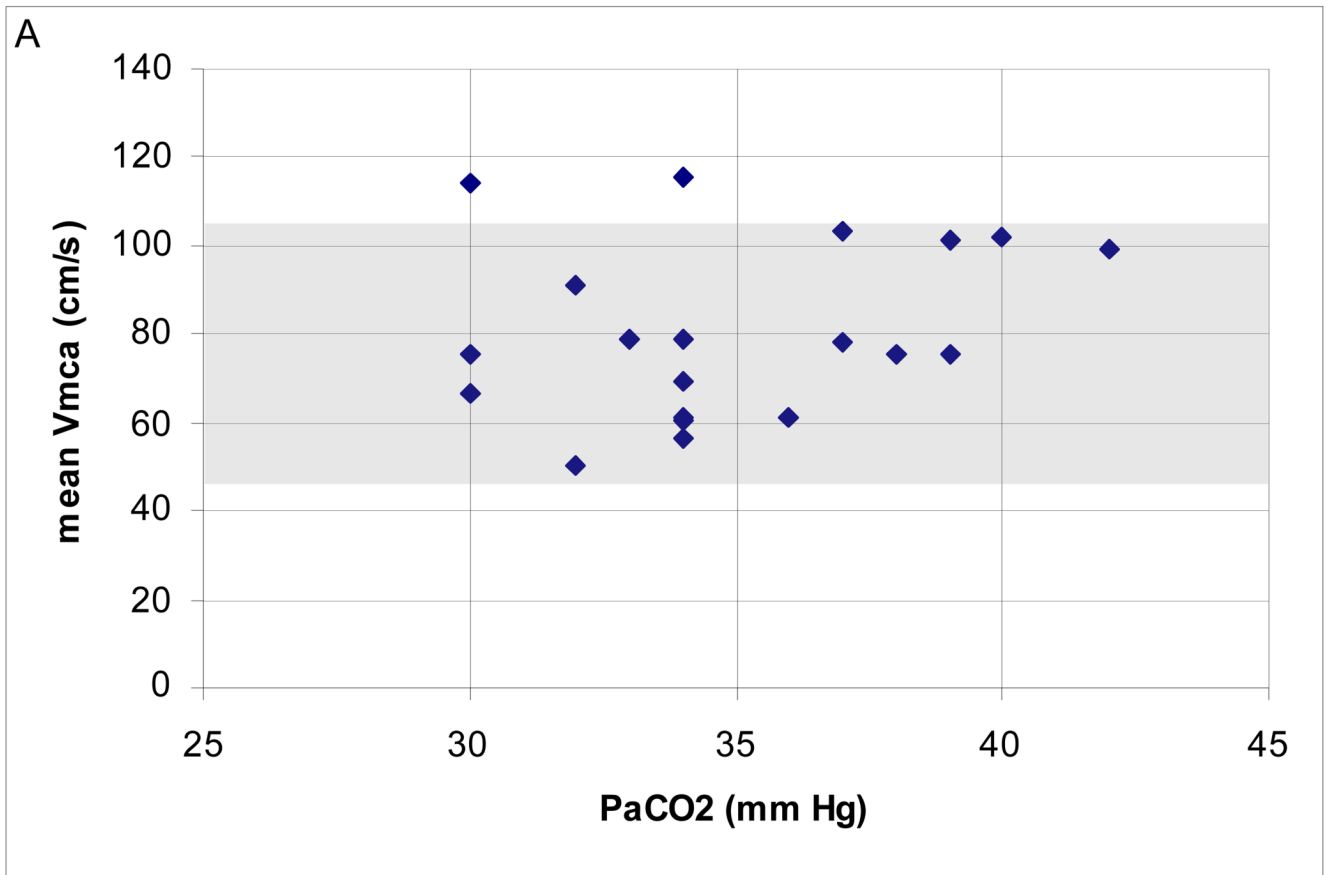


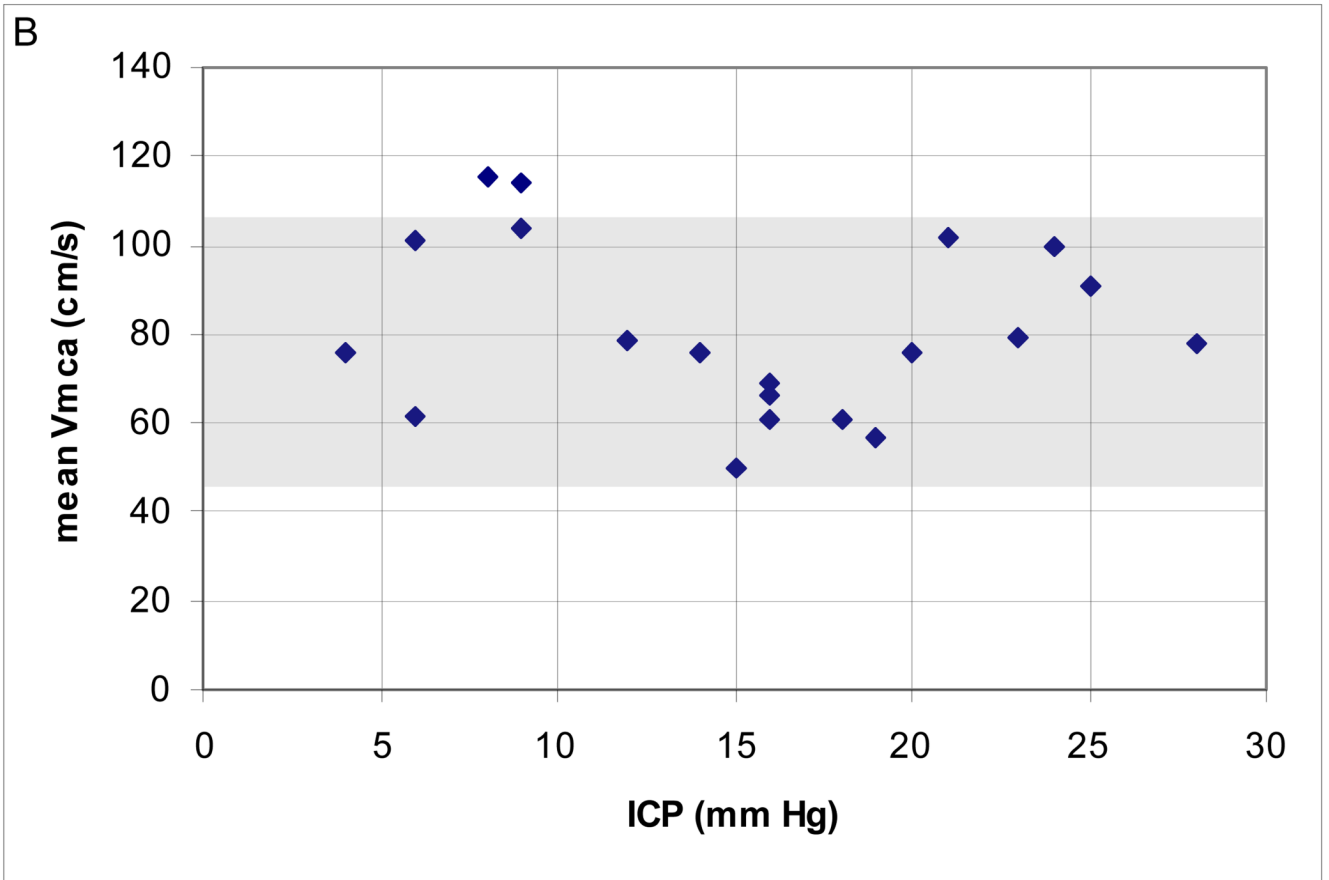


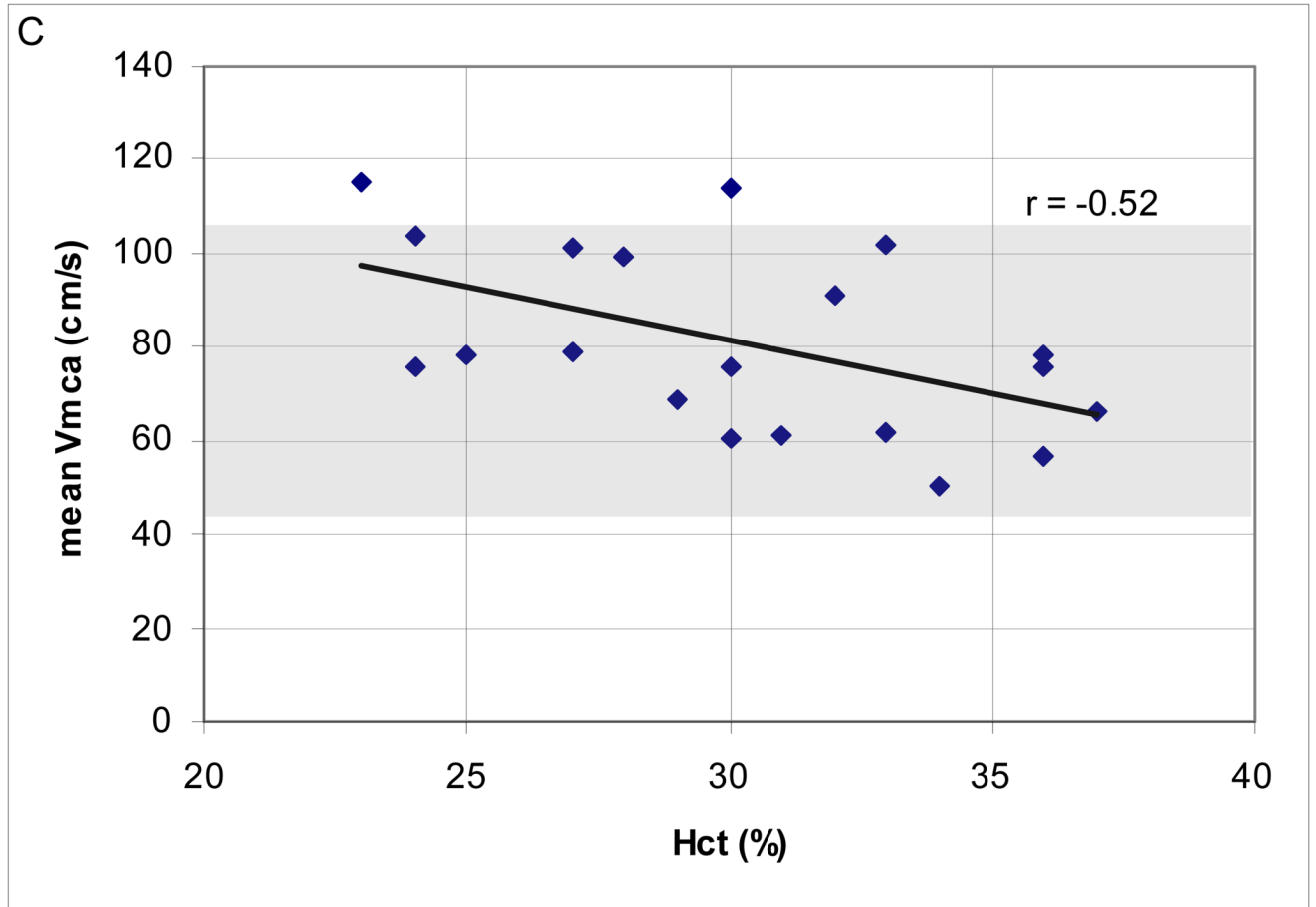
**Figure 1.**

(A–B). Relationship between cerebral perfusion pressure (CPP) and middle cerebral artery mean flow velocity ( $V_{mca}$ ) in children post-TBI between ages 10–16.9 years. ICP (mmHg) data are presented for the two patients whose  $V_{mca}$  are high for age and gender. (A)  $N = 20$  boys. Normal  $V_{mca}$  (cm/s)  $75 \pm 16$  (43–107)\*\* for age and gender denoted by shaded area. Mean  $V_{mca}$  (cm/s)  $77 \pm 22$  (32–123). Mean CPP (mm Hg)  $66 \pm 16$  (34–87). Spearman's  $\rho = -0.08$ ;  $p = 0.7$ . (B)  $N = 3$  girls. Normal  $V_{mca}$  (cm/s)  $89 \pm 16$  (57–121)\*\* for age and gender denoted by shaded area. Mean  $V_{mca}$  (cm/s)  $79 \pm 37$  (52–134). Mean CPP (mm Hg)  $59 \pm 22$  (31–83).

\*\*Source: Vavilala et al., 2005 [17] and Tontisirin et al., 2007 [18]









**Table 1**

Clinical data of 42 children with severe traumatic brain injury. Data are presented as mean  $\pm$  SD (range) or n (%).

<b>Age (years)</b>	8.9. $\pm$ 5.2 (0.8–16.0)
<b>Male</b>	30 (71)
<b>Admission Glasgow coma scale</b>	4 $\pm$ 1.2 (3–7)
<b>Mechanism of injury</b>	
Motor vehicle crash	11 (26)
Fall	11 (26)
Auto-pedestrian	4 (10)
Inflicted trauma	3 (7)
Bike	6 (14)
Gun shot wound	3 (7)
Other	4 (10)
<b>Associated injuries*</b>	
Orthopedic	13 (31)
Abdominal/pulmonary	16 (38)
None	16 (38)
<b>Traumatic brain injury on computed tomography in emergency department**</b>	
Diffuse axonal injury	4 (9)
Subdural hematoma	20 (48)
Epidural hematoma	7 (15)
Subarachnoid hemorrhage	18 (43)
Intracerebral hemorrhage	8 (18)
Cerebral edema	9 (19)
Skull fracture	22 (52)
Cerebral infarction	1 (2)
<b>In-hospital mortality</b>	2 (4)

\* Percentages exceed 100% because some patients have multiple injuries.

**2A and 2B.** Relationship between cerebral perfusion pressure (CPP) and middle cerebral artery mean flow velocity ( $V_{mca}$ ) in 42 children with CPP > 40 mm Hg. Cerebral autoregulation available in only 27 patients. Low mean  $V_{mca}$  =  $V_{mca}$  < 2SD and high mean  $V_{mca}$  =  $V_{mca}$  > 2SD for age and gender. ICP = intracranial pressure. Hct = hematocrit. (A) Data are presented as mean  $\pm$  SD (range). (B) Data are presented n (%).

Table 2

	Low mean $V_{mca}$		High mean $V_{mca}$	
	(n=4; 9%)	p	Normal mean $V_{mca}$ (n=33; 79%)	(n=5; 12%)
PaCO <sub>2</sub> (mm Hg)	33 $\pm$ 5 (29–40)	0.51 <sup>‡</sup>	35 $\pm$ 3 (30–42)	36 $\pm$ 4 (30–39)
ICP (mm Hg)	16 $\pm$ 16 (5–40)	0.97 <sup>‡</sup>	15 $\pm$ 7 (4–28)	17 $\pm$ 5 (12–25)
CPP (mm Hg)	59 $\pm$ 4 (54–63)	.09 <sup>‡</sup>	64 $\pm$ 14 (43–87)	57 $\pm$ 11 (42–70)
Hct (%)	35 $\pm$ 5 (29–42)	0.21 <sup>‡</sup>	30 $\pm$ 4 (23–37)	25 $\pm$ 4 (21–30)

	Low mean $V_{mca}$		High mean $V_{mca}$	
	(n=4; 9%)	p	Normal mean $V_{mca}$ (n=33; 79%)	(n=5; 12%)
Number of patients with PaCO <sub>2</sub> < 35 mm Hg	3(75)	0.41 <sup>‡</sup>	18(55)	2(40)
Number of patients with ICP > 20 mm Hg	1(25)	0.66 <sup>‡</sup>	10(30)	1(20)
Number of patients with temperature > 38.5°C	0(0)	--	5(15)	2(40)
Number of patients who received sedation	3(75)	0.59 <sup>‡</sup>	27 (82)	4(80)
Number of patients with impaired autoregulation (N=10/27)	3(75%)	0.08 <sup>‡</sup>	4(22%)	3(60%)
Median CPP (mm Hg) in patients with impaired autoregulation	58	--	78	64

\* Source: Bode, 1988 [16]

\*\* Source: Vavilala et al., 2005 [17] and Tontisirin et al., 2007 [18]

<sup>‡</sup> p value: values vs. Normal for each category.