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## Impact of Methamphetamine on Regional Metabolism and Cerebral Blood Flow after Traumatic Brain Injury

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## Abstract

Substance abuse is a frequent comorbid condition among patients with Traumatic Brain Injury (TBI), but little is known about its potential additive or interactive effects on tissue injury or recovery from TBI. This study aims to evaluate changes in regional metabolism and cerebral perfusion in subjects who used methamphetamine (METH) prior to sustaining a TBI. We hypothesized that METH use would decrease pericontusional cerebral perfusion and markers of neuronal metabolism, in TBI patients compared to those without METH use.

**Methods**—This is a single center prospective observational study. Adults with moderate and severe TBI were included. MRI scanning was performed on a 3 Tesla scanner. MP-RAGE and FLAIR sequences as well as Metabolite spectra of NAA and lactate in pericontusional and contralateral voxels identified on the MP-RAGE scans. A spiral-based FAIR sequence was used for the acquisition of cerebral blood flow (CBF) maps. Regional CBF images were analyzed using Image J open source software. Pericontusional and contralateral CBF, NAA and lactate were assessed in the entire cohort and in the METH and non-METH groups.

**Results**—17 subjects completed the MR studies. Analysis of entire cohort: Pericontusional NAA concentrations ( $5.81 \pm 2.0$  mM/kg) were 12% lower compared to the contralateral NAA ( $6.98 \pm 1.2$  mM/kg;  $p=0.03$ ). Lactate concentrations and CBF were not significantly different between the two regions, however, regional cerebral blood flow was equally reduced in the two regions. Subgroup analysis: 41% of subjects tested positive for METH. The mean age, Glasgow Coma Scale and time to scan did not differ between groups. The two subject groups also had similar regional NAA and lactate. Pericontusional CBF was 60% lower in the METH users than the non-users,  $p=0.04$ ; contralateral CBF did not differ between the groups.

**Conclusion**—This small study demonstrates that tissue metabolism is regionally heterogeneous after TBI and pericontusional perfusion was significantly reduced in the METH subgroup.

## Keywords

Adult brain injury; MRI; blood flow; metabolism; alcohol and drug abuse

## Introduction

Traumatic brain injury (TBI) is a significant public health problem in the United States and around the world. Approximately, 1.5 million cases of TBI occur in the US each year. Fifty thousand of these victims die and 80,000 survive with moderate to severe cognitive and motor disability.<sup>1,2</sup> The Centers for Disease Control and Prevention (CDC) estimates that the annual cost of TBI per year in the United States is 56.3 billion dollars.<sup>3</sup> The occurrence of TBI is often linked to substance abuse, which increases risk taking behavior and leads to more severe TBI.<sup>4</sup> As a consequence, 36–51% of victims of traumatic brain injury are found to be using illicit drugs.<sup>5,6,7</sup> Worldwide 15 million people regularly use amphetamines<sup>8</sup>, and in particular methamphetamine (METH), a highly addictive drug of abuse that has been increasing in popularity in the US and around the world.<sup>9</sup> METH is toxic to the dopaminergic neurotransmitter system<sup>10,11</sup> and has systemic hemodynamic effects.<sup>12</sup>

Since little is known about the effects of METH in patients with TBI, a study was initiated to assess for metabolic and perfusion changes in patients who used METH prior to sustaining a TBI.

Brain metabolism was evaluated non-invasively, using proton MR spectroscopy ( $^1\text{H}$  MRS), an important tool in the evaluation of tissue metabolic state after TBI.<sup>13,14,15,16</sup>  $^1\text{H}$  MRS can non-invasively provide information about several important chemicals in the brain. Of particular interest in the context of TBI are N-acetyl-aspartate (NAA), a marker of neuronal cell function, and lactate, which may be elevated when aerobic metabolism is compromised.<sup>15</sup> Additionally, cerebral blood flow is a quantifiable physiological parameter that can be measured by MRI techniques. Cerebral blood flow is altered after TBI, and pericontusional tissue seems to be at highest risk.<sup>17</sup> Furthermore, METH significantly elevates synaptic dopamine levels.<sup>10,18</sup> Since dopaminergic nerve terminals on blood vessels can cause vasomotor changes of brain microvasculature<sup>19</sup> patients who used methamphetamine prior to sustaining a TBI may have more profound alterations in regional tissue perfusion. Therefore, we hypothesized that METH use would further the decreases in pericontusional cerebral perfusion and NAA concentrations, as well as increases in lactate concentration in TBI patients compared to those without METH use.

## Methods

This protocol was reviewed and approved by the institutional research review committee at The Queen's Medical Center. The study is a single center prospective observational study evaluating the effects of METH on cerebral metabolism and perfusion in patients with moderate or severe TBI. Subjects were screened between October, 2007 and May, 2009. Subjects were screened by the neurointensivist on call and informed consents were obtained from the surrogate decision makers. Inclusion criteria include: age between 18 and 65 years, traumatic brain injury with post resuscitation Glasgow Coma Scale < 13, informed consent provided and signed by a surrogate decision maker. Exclusion criteria include: profound hypoxia (apnea in field or PaO<sub>2</sub> < 60mmHg), sustained hypotension with systolic blood pressure (SBP) < 90 mmHg, MRI incompatible device or implant, any preexisting neurologic, psychiatric or systemic disorder that might alter CBF or metabolism, or pregnancy. Incarcerated patients were not included and neither were those with penetrating brain injury. All patients received standard clinical care in accordance with the Brain Trauma Foundation.<sup>20</sup> Fifty eight patients were screened, 20 subjects were enrolled and 17 underwent MRI imaging. Reasons for screen failure included the following: surrogate decision maker unavailable or unwilling to consent to study, GCS improved to > 13, Uncontrolled hypoxia or hypotension documented, previous traumatic brain injury, pacemaker or other MRI incompatible device.

## MRI scanning

Subjects who were clinically stable for MRI scanning within the first 30 days post injury were transported to the University of Hawaii/QMC MR Research Center when medically stable enough to tolerate the supine head position without increased intracranial pressure. Intracranial and hemodynamic monitoring was continued while the subject was in the MR

scanner if necessary. ICP monitoring during MRI scanning was performed using a standard tunneled ventriculostomy catheter with a fluid coupled pressure transducer. Subjects with intracranial monitors inserted through a cranial bolt system underwent MRI scanning after the monitor was removed. An ICU nurse and a respiratory therapist, as well as a research nurse and an investigator accompanied each subject. All these personnel could continue to monitor and treat cerebral and hemodynamic abnormalities if they arose during the scan. MRI scanning was performed on the research-dedicated Siemens MAGNETOM Trio, a 3 Tesla Tim system scanner (Erlangen, Germany), using an 8-channel array head coil. The total MR acquisition time was less than one hour. Low dose midazolam and opiate analgesia were used as needed, but subjects did not receive propofol during scanning.

### Structural MRI

Following a localizer scan, a high-resolution sagittal 3D magnetization-prepared rapid gradient echo (MP-RAGE) sequence with whole-brain coverage was acquired (TE/TR/TI 4.9ms/2.2s/1s, 12 degrees flip angle, image matrix 256×256×144, isotropic 1mm resolution. Next, a fluid-attenuated inversion recovery (FLAIR) sequence with T2 contrast was acquired for the detection of cerebral contusions (axial, TE/TR/TI 85ms/10s/2.5s; image matrix 320×256; FOV 220×176 mm<sup>2</sup>; 3–4mm slices without gap; in-plane-resolution 0.7mm).

### <sup>1</sup>H MRS

A short echo-time Point RESolved Spectroscopy (PRESS) sequence was used to localize 2 voxels (4cc each) on the MP-RAGE scans which were in areas of white matter pericontusional and contralateral to cerebral contusions. Spectra were acquired at short echo time (TE = 30ms, TR = 3s, 64 averages, 2kHz bandwidth, 2K data points), followed by the acquisition of fully-relaxed (TR = 10s) unsuppressed water FIDs at 8 different echo times (TE = 30ms to 1s). These data allowed calculation of metabolite concentrations corrected for the partial volume of cerebral spinal fluid within the voxels.<sup>15</sup> Spectra were fitted with a customized version of the LC model program<sup>21</sup>, which models each in vivo spectrum as a linear superposition of ideal individual metabolite spectra, including those of NAA and lactate.

### Perfusion MRI

A spiral-based flow-sensitive alternating inversion recovery (FAIR) sequence was used for the acquisition of cerebral blood flow (CBF) maps.<sup>22,23</sup> The sequence parameters were TI = 1200 ms, TE = 3 ms, TR = 2 sec, 22 cm FOV, 128×128 matrix, 8 interleaves; 10 repeats; 10 5 mm slice pairs, and a 5:20 scan time. A T1 map for CBF quantification was also acquired using the spiral sequence with the same parameters except TI = 50, 100, 500, 1000, 3000, and 5000 ms; 4 interleaves; TR = 7 sec; no repeats; and a 2:48 scan time. We estimated CBF (ml/g tissue/s) using the method previously reported by.<sup>24</sup> Regional CBF images from the FAIR studies were analyzed using Image J open source software.<sup>25</sup> Two control subjects were scanned initially to establish a range of normal CBF. For the TBI subjects regional CBF was determined in regions of interest that were manually drawn to match the voxels from the <sup>1</sup>H MRS scans. Pericontusional areas were assigned by drawing a 2 cm rim around the area of cerebral contusion as previously described by Steiner et al.<sup>26</sup> (Figure 1)

All subjects underwent urine toxicology testing on admission as part of routine clinical care. This urine test detected recent use of cocaine, phencyclidine, methamphetamine, benzodiazepines and opiates, Marijuana and Alcohol. The cutoff level of methamphetamine detected is 500 ng/ml. This typically indicates use within the past 24 to 72 hours depending on factors such as amount taken, fluid intake, and urinary pH. An effort to obtain further history regarding drug from subject's friends and family was made. However, this was not consistently available to allow stratification of subjects by severity of substance abuse. Unfortunately, it was not possible to obtain an accurate drug use history in most subjects because the subjects were severely injured and unable to communicate. Additionally, most friends and family did not know for certain the exact extent of the subject's drug use history.

Pericontusional and contralateral CBF, NAA and lactate were assessed in the entire cohort and in the METH and non-METH groups. Independent sample t-tests were used to compare group differences; statistical significance was met with  $p < 0.05$ . Statistical analysis was performed using SPSS Version 19.

## Results

Twenty subjects were enrolled in the study over a period of two years, and 17 successfully completed the MR studies. The other 3 subjects remained medically unstable throughout the scanning window and did not complete the MRI protocol. Blood flow data were not available on four subjects due to technical problems, and pericontusional spectra in one subject were unacceptable due to an artifact from blood in the nearby contusion. **Data are shown in Table 1**

### Analysis of the entire cohort of TBI patients (Table 1, Figure 2)

Pericontusional NAA concentrations ( $5.81 \pm 2.0$  mM/kg) were 12% lower compared to the contralateral NAA ( $6.98 \pm 1.2$  mM/kg;  $p=0.03$ , two-tailed t-test,  $d = 1.22$ , large effect size). Lactate concentrations were not significantly different between the two regions ( $d = 0.71$ , moderate effect size). However, a moderate effect size ( $d = 0.71$ ) indicates that this non-significant result may be attributed to small sample size. Regional cerebral blood flow (rCBF) was equally reduced in the two regions compared to two control subjects who were scanned twice with 30 minutes in between studies. We found rCBF of  $50 (+/- 10)$  cc/100g/min and  $57 (+/- 8)$  cc/100g/min in control subject 01 and CBF of  $52 (+/- 12)$  cc/100g/min and  $54 (+/- 12)$  cc/100g/min in control subject 02.

### Analysis of subgroups based on METH status (Table 2, Figures 3 and 4)

41% of the subjects tested positive for METH. The mean age, Glasgow Coma Scale and time to scan did not differ significantly between the subjects with or without METH use. The two subject groups also had similar regional NAA or lactate. Pericontusional blood flow was 60% lower in the METH users than the non-users,  $p=0.04$  ( $d = 1.18$ , large effect size); however, contralateral CBF did not differ between the groups ( $d = 0.57$ , moderate effect size).

## Discussion

### Brain metabolism and perfusion in TBI patients

Our findings validate prior reports that patients with TBI showed greater metabolic abnormalities in the pericontusional brain regions, but the perfusion changes were decreased in both the pericontusional and contralateral brain regions. In addition, the major findings of this study are that the subgroup of TBI patients who tested positive for METH displayed a different pattern of tissue metabolism and regional perfusion when compared with those who tested negative. This is potentially of great importance to regional tissue recovery after TBI through METH's effects on tissue perfusion and metabolism.

Traumatic brain injury is associated with severe alterations in tissue metabolism and blood flow. These abnormalities occur in mild as well as severe TBI, which begin at the time of injury and continue through the subsequent hours and days.<sup>28</sup> Tissue near areas of injury (pericontusional) often behaves differently than tissue remote from focal injury. Cerebral microdialysis, positron emission tomography (PET), and <sup>1</sup>H MRS<sup>16,29</sup> have been used to study pericontusional tissue and changes in brain tissue metabolism. Cerebral microdialysis has demonstrated increased lactate-pyruvate ratios in pericontusional regions indicating greater cellular distress.<sup>30</sup> Our <sup>1</sup>H MRS findings demonstrate that as a group, our TBI subjects showed lower pericontusional NAA concentration relative to the contralateral NAA. The reduced NAA is consistent with the current literature indicating greater neuronal dysfunction in the pericontusional regions<sup>16,31</sup>, since declines in NAA levels are observed with cell death<sup>31</sup>, as well as mitochondrial dysfunction.<sup>32</sup> The primary role of NAA is to serve as a molecular water pump for neurons.<sup>33</sup> Water produced by glucose metabolism is then coupled to the movement of NAA along its intracellular-extracellular gradient. Thus NAA plays an important role in cellular metabolism. However, acutely decreased NAA level in the setting of TBI reflects only the severity of tissue injury, it cannot determine the ultimate tissue outcome, since some changes in NAA may reflect transient mitochondrial dysfunction.<sup>34</sup>

Cerebral lactate is also a useful marker of energy metabolism since elevated lactate levels indicate cerebral ischemia or mitochondrial failure.<sup>29</sup> Our TBI subjects showed only a trend for higher lactate on <sup>1</sup>H MRS in the pericontusional brain regions compare to the contralateral region. Since we do not have normal controls for comparison, we cannot determine whether the contralateral brain region also showed higher than normal lactate. Nevertheless, the tendency for higher lactate in the pericontusional region is consistent with a prior MRS study of TBI patients, and which suggests a failure of oxidative metabolism.<sup>16</sup>

The greater metabolic abnormalities in the pericontusional regions are also consistent with <sup>15</sup>O-PET studies that found decreased pericontusional perfusion in patients after TBI without the expected compensatory increase or augmented cerebral perfusion pressure. The abnormal perfusion response suggests that pericontusional tissue is not able to compensate for fluctuations in perfusion and is more vulnerable to ischemic secondary injury.<sup>17,26</sup> However, in our current study, both the pericontusional and contralateral regions of our entire cohort of TBI subjects showed decreased rCBF (~15 cc/100g/ min), which is significantly lower than the normal CBF is about 54 ±12 cc/100 gm/ min.<sup>27</sup> These findings

are consistent with prior reports that describe an acute decrease in global and regional CBF after TBI, with slow normalization of CBF over time (days to weeks).<sup>28,35</sup> The degree of decrease in CBF after TBI is variable depending on the region sampled. PET imaging has demonstrated CBF as low as 11 cc/ 100g/ min in pericontusional areas and as high as 46 cc/ 100g/min in remote areas with healthy controls showing 49 cc/100g/min.<sup>36</sup>

### Effects of METH on TBI brain metabolism and perfusion

In a non- trauma population, methamphetamine use has been associated with changes in brain perfusion and metabolism. Magnetic resonance spectroscopy studies in METH users indicate changes in glial markers (choline and myoinositol) as well as the neuronal marker NAA.

A study in abstinent METH users showed persistently lower than normal ratios of NAA to total creatine in the anterior cingulate cortex regardless of the time since last use.<sup>30</sup> Perfusion MRI studies in abstinent METH users also showed altered regional CBF, with decreased relative blood flow in bilateral putamen and the right parietal region, but increased relative perfusion in temporoparietal white matter and left occipital cortex.<sup>9</sup> A study using SPECT imaging in short term and long-term abstinent METH users also showed decreased regional CBF in the right anterior cingulate cortex.<sup>37</sup>

In the METH vs. non-METH analysis our findings demonstrate that the main difference between subjects who tested positive for METH and those who tested negative was lower pericontusional CBF in the METH-positive group. Likewise, the METH subjects showed a trend for larger regional differences in CBF with the pericontusional rCBF being the lowest. However, we did not observe an alteration in tissue metabolism between METH users and non-users, either in NAA or lactate.

This disconnection between tissue perfusion and metabolism after TBI has been previously described. Several authors described findings that suggest a non ischemic etiology for the metabolic markers of cellular distress after TBI. In subjects who underwent PET scanning and simultaneous microdialysis monitoring after TBI, Vespa et al demonstrated that the metabolic markers of cellular distress were much more frequently found than true ischemia seen on quantitative PET scanning.<sup>29</sup> More recently, Soustiel et al performed ultrasound CBF studies and AVDO<sub>2</sub> calculations to measure CMRO<sub>2</sub> on patients after decompressive hemicraniectomy after TBI. They demonstrated that although the decompressive craniectomy only improved the rCBF but not the metabolic dysfunction of the tissue. Therefore, direct ischemia may not be responsible for the metabolic alterations seen after TBI.<sup>38</sup> Similarly, we may not see the expected metabolic alterations in areas of low pericontusional rCBF because changes in rCBF may not be the predominant factor driving the metabolic dysfunction.

There are several important limitations to this study. First of all, the study is underpowered . Ideally we planned to enroll 30 subjects for 90% power to detect a 10% decrease in NAA and a 10% decrease in CBF. Unfortunately, we were unable to reach our enrollment target due to the challenges of performing acute MRI studies on severely injured subjects. Also, the heterogeneity of the clinical TBI group with varying severity of injury and regions of

structural brain injury as well as the diverse injury mechanisms create variability in the data particularly in such a small sample. Additionally, the test used to demonstrate METH use was a urine test which was only reported as positive or negative and could not measure a specific concentration. It is not possible to determine when the subject last used the drug or how much they had used. Additionally, because the subjects were comatose and their families often did not know the previous drug use history it was impossible to separate those with a history of METH use from those who had used the drug only once. Therefore the study can only describe an effect of acute METH use coincident with a TBI. Although the average time to MRI scanning did not differ between the METH and non-METH groups, there was considerable variability in the time of MR scanning since the TBI (range 2–27 days). Changes in tissue chemistry after TBI are quite dynamic over time, and might have contributed to the variability of findings across subjects. For instance, rCBF can be low initially with gradual recovery, and transmembrane ion fluxes, excitotoxicity and electrical depolarizations can occur for several days post injury and are dynamic over time.<sup>35,28</sup> Therefore, we would expect that the exact tissue response or recovery at the time of MR scanning was not equivalent across subjects, which might have influenced measurements of tissue perfusion and metabolism. However, we were successful in controlling variability due to sedation, pCO<sub>2</sub> levels and blood pressure during MR scanning. There was also no difference in the range of time between TBI and MR scanning in the METH vs. nonMETH groups.

In conclusion, this small study demonstrates that tissue metabolism is regionally heterogeneous after TBI. The pericontusional NAA, which is a marker of neuronal injury, tended to be lower than the NAA in the contralateral hemisphere. Likewise, rCBF was reduced in both hemispheres in these TBI subjects. However, when the METH cohort was compared to the nonMETH cohort rCBF was significantly reduced in the pericontusional tissue. We did not observe any regional difference in tissue metabolism in the METH cohort, which may be due to the relatively small sample sizes of the subgroups.

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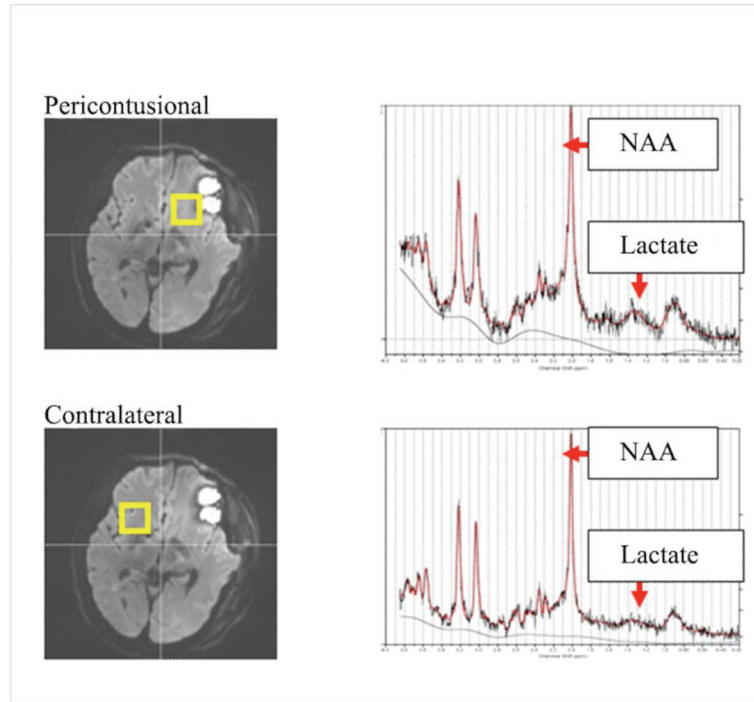
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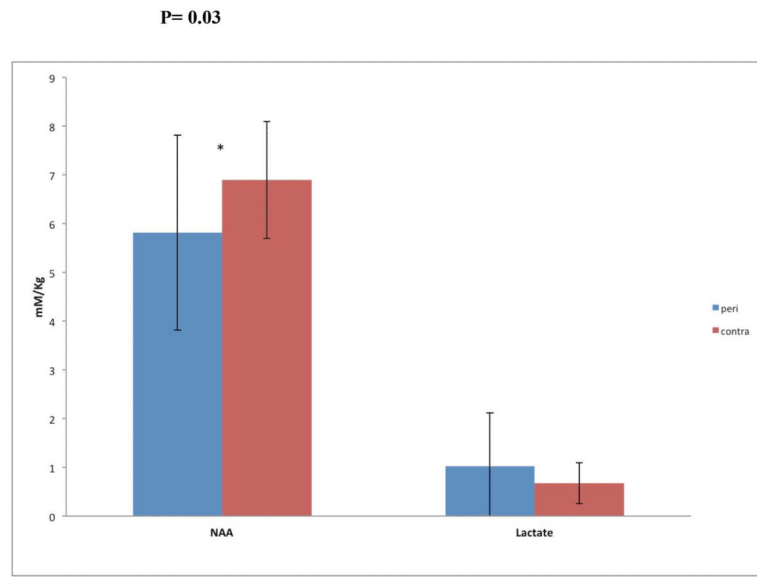


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**Figure 1.**  
voxel location



**Figure 2.**  
MR spectroscopy for all TBI subjects

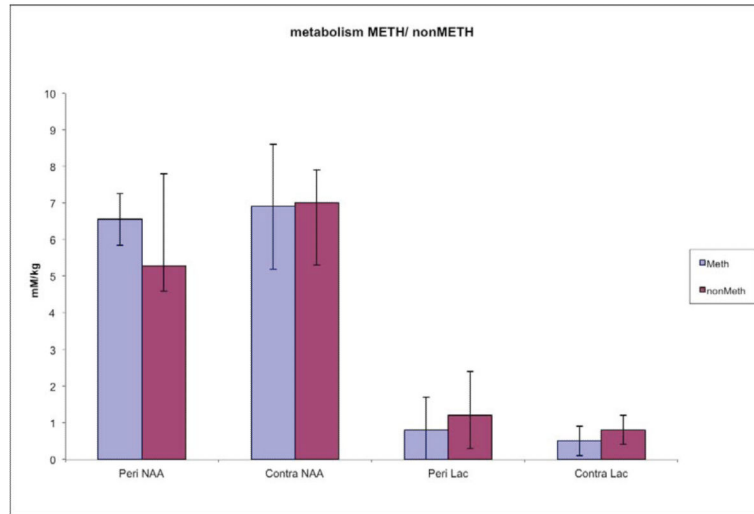
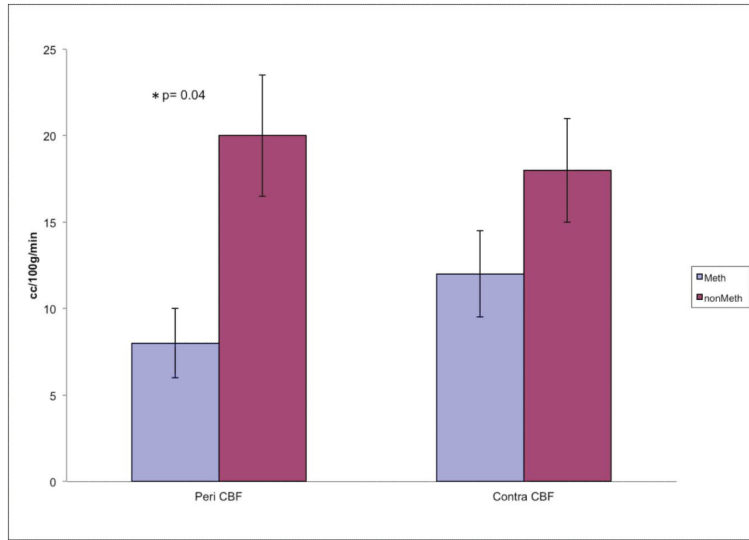


Figure 3.



**Figure 4.**  
Regional Cerebral Blood flow in Meth vs Non Meth

Table 1

MRI data for all TBI subjects

Pt	Age years	G	METH	GCS	TTS days	pNA A mM/kg	cNA A mM/kg	pLac mM/kg	cLac mM/kg	pCBF cc/10 0g/min	cCBF cc/10 0g/min
1	58	M	Yes	9	7	6.025	5.824	1.669	0.207	-	-
2	33	M	Yes	5	4	6.083	8.253	0.571	0.342	-	-
3	37	M	No	3	2	7.607	8.17	0.069	1.037	41	28
4	42	M	No	5	3	7.675	8.763	0.911	0.748	20.7	27.3
5	21	F	Yes	7	10	7.96	7.014	0.3	0.935	20.3	38
6	56	F	No	6	11	-	6.353	-	0.156	25.4	27.7
7	48	M	Yes	7	17	5.848	5.259	2.466	0.274	12.4	15.6
8	21	M	No	7	17	5.805	6.527	0.649	0.449	10.3	12.4
9	48	M	No	6	4	6.708	7.342	0.576	0.881	16.3	15.5
10	46	M	No	8	18	6.84	6.73	1.322	0.482	23.0	24.1
11	30	F	Yes	8	27	6.656	4.85	0.068	0.604	13.3	17.2
12	49	F	Yes	5	4	6.701	9.469	0.055	1.135	-	-
13	49	F	No	7	10	4.859	7.486	2.488	0.563	-	-
14	18	M	No	7	11	5.855	6.223	0	0.921	31.8	18.3
15	37	M	No	5	10	5.548	6.659	3.346	1.702	16.2	12.4
16	21	M	No	7	15	2.002	5.987	2.832	0.769	11.3	14
17	54	M	Yes	7	8	6.589	7.66	0.532	0.118	10.7	12.4

Summary data	Mean 39	M:F 12:5	Y:N 7:10	Mean 6.4	Mean 10	5.81±2.0, 6.89±1.2 p=0.03	1.02±1.1, 0.67±0.42 p=0.17	15±12, 15±11 p= 0.72
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GCS- Glasgow Coma Scale, G- gender, TTS – time to scan in days, p- pericontusional c- contralateral, NAAA- N- acetyl-aspartate, Lac- lactate, NA –not available, p- pericontusional c- contralateral, CBF- cerebral blood flow measures in 13 subjects only, METH- positive urine toxicology for methamphetamine on admission

**Table 2**

TBI patients who had METH positive versus METH negative urine tests

	All subjects	p-value	METH positive	METH negative	p-value
Sample size (N)	17		7	10	
Mean Age (years)	39 (18–58)		42 ± 14	38 ± 13	0.52
Glasgow Coma Scale	6.4 ± 1.46		6.8 ± 1.5	6.1 ± 1.5	0.31
M:F	12:5		4:3	8:2	
Time to scan (mean)	10 days		11 days	10 days	0.79
[NAA] mM/kg		0.03			
Pericontusional	5.81 ± 2.0		6.55 ± 0.7	5.29 ± 2.5	0.21
Contralateral	6.89 ± 1.2		6.9 ± 1.7	7.0 ± 0.9	0.85
[Lactate] mM/kg		0.17			
Pericontusional	1.02 ± 1.1		0.8 ± 0.9	1.2 ± 1.2	0.47
Contralateral	0.67 ± 0.42		0.5 ± 0.4	0.8 ± 0.4	0.23
rCBF (cc/100g/min)		0.72			
Pericontusional	15 ± 12		8 ± 8	20 ± 12	0.04*
Contralateral	15 ± 11		12 ± 14	18 ± 9	0.29

NAA- N- acetyl-aspartate, CBF- cerebral blood flow, M:F- male: female METH positive- positive urine toxicology for methamphetamine on admission

\* statistical analysis performed on 13 subjects