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L-Arginine Reactivity in Cerebral Vessels After Severe Traumatic Brain Injury

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Abstract

Objectives—Traumatic brain injury (TBI) causes an early reduction of cerebral blood flow (CBF). The purpose was to study cerebrovascular endothelial function by examining the reactivity of cerebral vessels to L-arginine.

Methods—Fifty-one patients with severe TBI were prospectively studied by measuring cerebral hemodynamics before and after the administration of L-arginine, 300 mg/kg at 12 hrs and at 48 hrs after injury. These hemodynamic measurements, using transcranial Doppler techniques, included internal carotid flow volume as an estimate of hemispheric cerebral blood flow, flow velocity in intracranial vessels, CO₂ reactivity, and dynamic pressure autoregulation using thigh cuff deflation and carotid compression methods. Changes in the hemodynamics with L-arginine administration were analyzed using a general linear mixed model.

Results—L-arginine produced no change in mean arterial pressure, intracranial pressure, or brain oxygenation. Overall, L-arginine induced an 11.3% increase in internal carotid artery flow volume ($p = .0190$). This increase was larger at 48 hrs than at 12 hrs ($p = .0045$), and tended to be larger in the less injured hemisphere at both time periods. The response of flow velocity in the intracranial vessels was similar, but smaller differences with administration of L-arginine were observed. There was a significant improvement in CO₂ reactivity with L-arginine, but no change in dynamic pressure autoregulation.

Discussion—The low response of the cerebral vessels to L-arginine at 12 hrs post-injury with improvement at 48hrs suggests that dysfunction of cerebrovascular endothelium plays a role in the reduced CBF observed after TBI.

Keywords

cerebral autoregulation; endothelial dysfunction; L-arginine; nitric oxide; traumatic brain injury

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INTRODUCTION

Traumatic brain injury (TBI) induces cerebrovascular dysfunction that can be manifested as a spectrum of clinical problems ranging from impaired pressure autoregulation to hypoperfusion and frank ischemia. The inability to normally regulate cerebral blood flow (CBF) causes the injured brain to be susceptible to secondary ischemic injury and may adversely influence the neurological outcome. Impairment of specific CBF regulatory functions also has been shown to alter the injured brain's responses to common therapeutic interventions, such as mannitol, hyperventilation, induced hypertension, and barbiturate coma.¹⁻⁴

Very early after injury (<12 hr post-injury), a globally reduced CBF < 18–20 ml/100g/min is usually associated with a very severe injury, refractory intracranial hypertension, and a high risk of early mortality.^{5,6} During this early time period, every 10ml/100g/min increase in global CBF is associated with a 3-fold increase in the chances of surviving the brain injury.⁵ In patients who survive the early post-injury period, global CBF usually gradually recovers and may even become elevated relative to cerebral metabolic requirements.⁷ Global hypoperfusion after the early post-injury period usually occurs as a result of secondary insults such as hypotension, intracranial hypertension, and hypocapnia. Focal ischemia may occur throughout the acute recovery in areas of contusions.⁸

Despite recovery of CBF after the early post-injury period, most patients with severe TBI have impaired autoregulation which may even worsen as CBF recovers and impaired autoregulation persists for many days after the initial injury.⁹ CO₂ reactivity is usually lowest in the early post-injury period and gradually recovers. Metabolic autoregulation has not been commonly studied after TBI, but some studies suggest that this regulatory mechanism is severely impaired during the first 2 weeks after injury.¹⁰

The mechanism of cerebrovascular dysfunction after TBI is probably multi-factorial. Experimental studies have implicated numerous vasoactive mediators and presence of oxidative stress, as well as obstruction of capillaries from platelet aggregations.¹¹⁻¹⁵ These mechanisms have not been well-studied in human TBI, but clinical studies measuring nitric oxide (NO) levels in CSF or in microdialysate fluids have suggested a role for NO in at least some of the cerebrovascular abnormalities.^{16,17} A better understanding of the underlying pathological mechanisms for the cerebrovascular dysfunction would be helpful in developing new therapies.

The purpose of this study was to assess cerebral vascular reactivity to L-arginine administration at 12 hr and 48 hr after a severe TBI. In addition to the response of CBF, the effects of L-arginine on CO₂ reactivity and on pressure autoregulation were assessed. L-arginine is metabolized by vascular endothelium to NO, which vasodilates intracranial vessels. Normally, a small increase in CBF occurs following an infusion of L-arginine. The change in CBF with L-arginine administration may provide an assessment of vascular endothelial function after a severe TBI.

MATERIAL AND METHODS

Patient Selection and Clinical Management

A total of 51 patients with severe TBI (motor component of Glasgow Coma Score [GCS] ≤ 5) admitted to Ben Taub General Hospital in Houston, Texas were studied (Table 1). Patients who arrived more than 12 hr after injury, who were GCS 3 with bilaterally fixed and dilated pupils, who were hypotensive after resuscitation, or who had unstable ICP were excluded from the study. The study was approved by the Institutional Review Board of the Baylor College of Medicine, and informed consent was obtained from the patients' families.

Upon arrival in the emergency room, patients immediately underwent intubation, hemodynamic stabilization, and resuscitation when necessary. Patients in whom an intracranial mass lesion was demonstrated on the initial computed tomography (CT) scan underwent an immediate neurosurgical procedure. Intracranial pressure (ICP), mean arterial blood pressure (MAP), end-tidal CO₂ (ETCO₂), arterial and jugular venous oxygen saturation (SaO₂ and SjvO₂), and brain tissue oxygen (PbtO₂) were monitored during the acute post-injury period. The PbtO₂ probe (LICOX; Integra Neurocare) was positioned in peri-contusional brain tissue when possible. Otherwise the PbtO₂ probe was placed in the white matter of the right frontal lobe. The goals of the early management were to keep ICP < 20 mm Hg and cerebral perfusion pressure (CPP) > 60 mm Hg, unless the SjvO₂ and/or PbtO₂ values indicated that a higher level of CPP was needed. Blood glucose levels were maintained between 100 and 180 mg/dl, and the goals for temperature were 36.5 – 37.5°C.

Study Protocol

L-arginine reactivity tests were performed at two different time periods: first at approximately 12 hours post-injury and again at 48 hours post-injury. All measurements were performed after resuscitation and surgical removal of mass lesions if needed. The 12 hr time period was chosen as a time when the patient is usually well-resuscitated but CBF is often still low, and the 48 hr time period was chosen because CBF has usually recovered but pressure autoregulation is typically at its nadir.⁹

Immediately before and after infusion of L-arginine, 300mg/kg intravenously over 30 minutes, the following parameters were obtained: ICP, MAP, ETCO₂, SaO₂, and several indices of cerebral perfusion (SjvO₂, PbtO₂, internal carotid artery flow volume [ICA-FV], flow velocity in the anterior cerebral artery [ACA-FV], middle cerebral artery [MCA-FV], posterior cerebral artery [PCA-FV], and internal carotid artery [ICA-FV], carbon dioxide reactivity [CO₂R], and dynamic pressure autoregulation) as well as blood and CSF samples for nitrate/nitrite levels. For the flow velocity and flow volume measurements, CO₂R, and dynamic pressure autoregulation parameters, both left and right sides were measured and these were designated as “best” or “worst” side depending on the appearance of the injury on the admission CT scan in the individual patient. The hemisphere with the most severe traumatic brain injury was designated the “worst” side.

ICA-FV was measured using an angle-independent dual-beam Doppler ultrasound device (FlowGuard, Cardiosonix Inc). ICA-FV measured with this device has good correlation with hemispheric cerebral blood flow measured using ¹³³Xenon clearance technique.¹⁸ The FV measurements were performed on a DWL MultiDop transcranial Doppler (Compumedics DWL, Singen, Germany). CO₂R was calculated by the following formula: CO₂R = (ΔMCA-FV * 100% / baseline MCA-FV) / ΔpCO₂. Dynamic pressure autoregulation was assessed by two different methods: the cuff deflation technique and the carotid compression technique.

For the cuff deflation method, the autoregulation index (ARI) was calculated by the method of Aaslid et al.¹⁹ Three determinations of ARI were averaged to give a single baseline value. Mean blood pressure and bilateral middle cerebral artery flow velocity were recorded continuously before and after a step drop in blood pressure. The thigh cuff deflation technique was used to induce the drop in blood pressure. Large bilateral thigh cuffs were inflated to 20 mmHg above the systolic arterial pressure for a period of 2 minutes. A transient blood pressure drop was induced by rapid deflation of the thigh cuffs. A drop in blood pressure of at least 12 mmHg was required to be considered a valid cuff deflation test.²⁰

An ARI ranging from 0 to 9 was calculated by the method proposed by Tiecks et al.²¹ and implemented in the DWL MultiDop transcranial Doppler software (Compumedics DWL, Singen, Germany). Briefly, the recorded flow velocity response to the cuff deflation was

compared with the 10 models constructed using the mean arterial pressure as the input function. Each model is generated from the arterial tracing by a specific combination of time constant, damping factor, and autoregulatory dynamic gain. The closest match was selected based on the highest correlation coefficient. Normal ARI using this method is 5.0 ± 1.1 .²¹

Dynamic pressure autoregulation was also assessed using carotid compression technique. The transient hyperemic response ratio (THRR) following release of unilateral carotid compression for 5 seconds was calculated by the method of Smielewski et al.²² Three determinations of THRR were averaged to give a single value. Normal values for THRR are mean 1.20 (95% confidence limits 1.17 to 1.24).²²

L-arginine reactivity was calculated from $\Delta FV * 100\% / \text{baseline FV}$. Other investigators have reported that the L-arginine reactivity in normal subjects averages $21.3 \pm 10.9\%$.²³

Blood and cerebrospinal fluid (CSF) samples were obtained for measurement of nitrate and nitrite (NOx) levels. The CSF samples were collected from ventriculostomy catheters that were placed for the purpose of monitoring intracranial pressure. These samples were analyzed using a multiwell plate fluorometric assay in which nitrate is converted to nitrite using nitrate reductase yielding total NOx which converts 2,3-diaminonaphthalene to a measureable fluorescent product, 1(H)-naphthotriazide (Caymen Chemical Company, Ann Arbor, MI).

Statistical Analysis

Physiological parameters before and after the administration of L-arginine at 12 and 48 hours after injury were analyzed using a general linear mixed model. The analysis method was chosen because the data were from multiple assessments over time. This model provides unbiased estimates of the random effect, flexibility in the choice of the variance-covariance structures of the model, and maximum likelihood estimation. There were two observations per day across two days. There was an effect of day, and effect of administration of L-arginine, and an interaction term that tested whether the difference with L-arginine administration varied significantly by day. In addition, the response of patients who were 50 years or older were compared to those who were less than 50 years old. Summary data are expressed as mean $\pm$ standard deviation.

RESULTS

Patient Demographics

The characteristics of the patients who were studied are summarized in Table 1. There was a predominance of males (76.5 %), with a mean age of 35 ± 14 years, and an initial GCS score of 6.4 ± 3.3 . Forty-two patients were less than 50 years old (average age 30.1 ± 9.7 years), and nine patients were 50 years or older (average age 57.8 ± 5.0 years). Initial head CT scans were classified by the Marshall CT classification²⁴ and revealed evacuated mass lesion in 24 (47.1 %) patients, type 1 and 2 diffuse injury in 20 (39.2%) patients and type 3 and 4 diffuse injury in 7 (13.7%) patients. The mass lesions included 16 with subdural hematomas, 4 with epidural hematomas, and 4 with contusions/intracerebral hematomas.

Baseline Physiology

The target time for the initial L-arginine reactivity test was 12 hours post-injury. The baseline measurements were performed at 12.8 ± 6.2 hr post-injury. The target time for the second reactivity test was around 48 hr post-injury. These measurements were performed at 48.4 ± 12.2 hr post-injury.

The baseline (pre-L-arginine) pressure and oxygenation variables for these two reactivity tests are summarized in Table 2. MAP was significantly higher, averaging 96 ± 13 mmHg, at 48 hr post-injury compared to 90 ± 13 mmHg at 12 hr post-injury. The remaining variables that were measured, including ICP, MAP, ETCO₂, pCO₂, SjvO₂, and PbtO₂, were not significantly different at baseline between the two different time periods. The only other statistically significant observation for the pre-L-arginine values was that age interacted with the changes in pCO₂ and ETCO₂ over time. Older subjects had higher values for ETCO₂ at 48 hr than younger subjects. Younger subjects had higher values for pCO₂ (by 1.3 mmHg) than older subjects at 12hr, but older subjects had higher values (by 4.3 mmHg) than younger subjects at 48hr.

Baseline (pre-L-arginine) cerebral hemodynamic variables are summarized in Table 3. There was significantly greater baseline flow velocity in the ACA, MCA, PCA, and ICA ($p < 0.0001$) at 48 hours compared to 12 hours after injury. The remaining hemodynamic variables measured, including FVol, ARI, THRR, CO₂R, were not significantly different at baseline between the two different time periods. The only other statistically significant finding for the baseline cerebrovascular variables was that older patients had higher ARI values than younger patients.

Changes Induced by L-Arginine Administration

Changes in the cerebral hemodynamic variables following the administration of L-arginine are summarized in Table 3. Overall L-arginine induced an 11.3% increase in ICA-FVol (L-arginine main effect, $p = 0.0190$), from 181 ± 4 to 202 ± 6 ml/min. The increase in ICA-FVol following L-arginine infusion was significantly larger at 48 hours than at 12 hours (L-arginine x day interaction, $p = 0.0045$). L-arginine increased ICA-FVol by 16.0% at 48 hr (181 ± 51 to 210 ± 65 ml/min) compared to 2.7% at 12 hr post-injury (184 ± 70 to 189 ± 59 ml/min) on the worst side and 22.2% at 48hr (175 ± 49 to 214 ± 75 ml/min) compared to 5.4% at 12hr post-injury (185 ± 58 to 195 ± 54 ml/min) on the best side. The difference between the response of worst and best side was not statistically significant.

L-arginine induced a small increase in FV in the cerebral vessels. ACA-FV increased by 8.6%, MCA-FV increased by 4.7%, and PCA-FV increased by 5.1%. There was no difference in the response of FV to L-arginine at 12 and 48 hours, and there was no consistent difference in the response of FV to L-arginine between the worst and best sides. Age had a significant interaction with the L-arginine reactivity over time for ICA-FV. At 12 hr post-injury, in younger patients ICA-FV increased by 5.6 cm/sec compared to only 0.6 cm/sec in older patients. At 48 hr post-injury, ICA-FV increased by only 0.4 cm/sec compared to 11 cm/sec in older patients.

The measures of dynamic pressure autoregulation (ARI and THRR) did not consistently change with L-arginine infusion. ARI tended to improve following L-arginine ($p = .0738$), while THRR tended to worsen ($p = .1713$). Neither of these changes was statistically significant.

CO₂R, however, consistently improved following the infusion of L-arginine ($p = 0.0002$), and the change was similar at the two time periods studied, as well as for the worst and the best sides. At 12 hr post-injury, CO₂R increased from 2.2 ± 1.5 to 3.0 ± 1.8 on the worst side, and from 2.1 ± 1.3 to 3.4 ± 2.1 on the best side. At 48 hr, CO₂R increased from 2.5 ± 1.5 to 3.3 ± 2.1 on the worst side, and from 2.4 ± 1.8 to 2.9 ± 1.9 on the best side.

The changes in CSF and serum NOx values are summarized in Table 4. At 12 hr post-injury, the CSF levels of NOx increased from 0.82 ± 0.40 μ mol/L to 1.01 ± 0.61 μ mol/L. The CSF NOx did not increase at 48 hr, and the serum NOx levels did not increase on either day.

The changes in pressure and oxygenation variables after the administration of L-arginine are summarized in Table 2. Despite the increase in ICA-FV_{ol} that occurred with L-arginine infusion, there were no consistent changes in PbtO₂ or S_{ijv}O₂, possibly because the baseline values were normal. There were also no significant changes in MAP, ICP, ET_{CO}₂, or p_{CO}₂ after the administration of L-arginine at either 12 or 48 hours post-injury.

Although MAP for the group was unchanged, one patient who required dopamine to maintain an adequate blood pressure and cerebral perfusion pressure, did become hypotensive during the L-arginine infusion. Blood pressure recovered when the L-arginine was stopped, and there were no adverse consequences from the transient hypotension. No other adverse events occurred with L-arginine infusion.

DISCUSSION

Use of L-arginine infusion to test vessel reactivity has been primarily in the study of chronic cerebrovascular disease,^{23,25–31} and less is known about what such findings might mean following an acute injury such as TBI. In normal subjects, infusion of L-arginine results in an average 18–22% transient increase in FV using transcranial Doppler techniques.^{25,31} Okamoto et al. demonstrated an effect of age on L-arginine reactivity in normal subjects, with older subjects (average age 70) having about 50% of the response as young subjects (average age 20).³²

Most previous studies have demonstrated a reduced L-arginine reactivity in patients with cerebrovascular disease and/or risk factors. In patients with cerebral infarction, L-arginine reactivity was significantly reduced compared to normal controls.^{27,30} In patients with cerebrovascular disease, L-arginine reactivity was inversely correlated with intima-media thickness of the carotid arteries.²⁸ In contrast with these studies, one study has reported an increased L-arginine reactivity in patients with cerebrovascular risk factors, including minor stroke and transient ischemic attacks.³¹

These findings in patients with cerebrovascular disease and the correlations with endothelial pathology have suggested that a reduced responsiveness to L-arginine reflects impaired endothelial function. However, this may not always be the case and the implications could differ with the underlying disease.

In experimental TBI studies, constitutive nitric oxide synthase activity decreases and levels of tissue nitric oxide rapidly decrease after injury in contused brain tissue. L-arginine administration during this early post-injury time period improves CBF and also restores tissue nitric oxide levels.^(Cherian et al., 2000; DeWitt et al., 1997) Because this improvement in CBF requires the L-isomer of arginine and the presence of endothelial nitric oxide synthase, it is likely that the vascular effect of L-arginine after traumatic injury is primarily through increasing activity of endothelial nitric oxide synthase.¹³ Reduced responsiveness to L-arginine after TBI could indicate that the cerebrovascular endothelium is too damaged to respond, that endothelial nitric oxide synthase activity is inhibited or uncoupled, or that the L-arginine is diverted to another competing pathway such as arginase.

Using ICA-FV_{ol} in the present study, L-arginine reactivity was significantly greater at 48 hr than at 12 hr, suggesting that the ability of the cerebral vasculature to respond to L-arginine improves over time after injury. This finding is consistent with most clinical studies of cerebrovascular function in TBI patients, where global CBF is lowest during the first 12 hr post-injury and tends to recover over time after injury.^{5–7}

For the ICA-FV response to L-arginine at 12 hr post-injury, a significant age effect similar to that observed by Okamoto et al. was observed, with greater reactivity to L-arginine occurring

in the younger patients.³² At 48 hr post-injury, the pattern was reversed with the older patients having greater reactivity to L-arginine. Age effects on the cerebrovascular response to TBI are well-known, with hyperemia being more prominent in younger patients, especially 3–5 days after injury when inducible nitric oxide synthase (iNOS) activity may play a role.³³ An age difference in CBF after TBI has been also been confirmed in experimental studies.³⁴ It is possible that by 48 hr post-injury, cerebral vessels are already vasodilated in younger patients as a result of vasoactive mediators including nitric oxide associated with inflammatory responses, and may not be able to dilate additionally with infusion of L-arginine.

Both FV and ICA-FVol were used to assess changes in blood flow in this study with somewhat different findings. FV can be influenced by both changes in blood flow and by changes in the diameter of the vessel. Since FVol is corrected for changes in vessel diameter, it should more closely represent blood flow changes and has been shown to closely correlate with hemispheric CBF.¹⁸ In controlled circumstances such as with dynamic autoregulation testing, changes in FV have been shown to reflect changes in blood flow. However, in this study some discrepancies were observed between the 2 measurements. Significant increases in ICA-FVol occurred with L-arginine administration at both 12 hr and 48 hr post-injury, and amount of the increase was significantly greater at 48 than at 12 hr. For FV in the various intracranial vessels, the change with L-arginine administration was smaller than for ICA-FVol, was greater for ACA and PCA vessels than for MCA vessels, and did not differ significantly at the two time points in any of the vessels tested. The baseline FV in all of the intracranial vessels tested was greater at 48 hr than at 12 hr post-injury, but there was no difference in the baseline ICA-FVol at the two time periods. These findings may result from the inherent differences in the two types of measurements (FV vs. FVol), or from differences in the vessels being tested, i.e. FV in the basal intracranial vessels vs. FVol in the ICA. The former explanation is more likely since ICA-FV measurements followed a pattern similar to the FV measurements in the intracranial vessels.

In addition to these effects on CBF, L-arginine administration had a very consistent effect on CO₂ reactivity. A number of experimental studies have suggested that nitric oxide plays a role in the diminished CO₂ reactivity that occurs after TBI.^{35,36} The findings in the current TBI study would be consistent with such a role. In a previous clinical study, patients with cerebrovascular risk factors and reduced CO₂ reactivity were also observed to have a significantly improved CO₂ reactivity following administration of L-arginine.³⁷

In contrast to CO₂ reactivity, L-arginine administration did not significantly alter pressure autoregulation. Experimental studies regarding the role of nitric oxide in pressure autoregulation are less clear. Most studies have suggested no role for nitric oxide in pressure autoregulation,³⁸ but some suggest at least some role for nitric oxide.^{39,40}

Some limitations of the methods in this study should be acknowledged. Since no control subjects were studied, the only normal values for L-arginine reactivity were those available in the published literature. However, techniques could have differed, and a slightly lower weight-based dose of L-arginine was used in the TBI patients to minimize the risk of hypotension (300 mg/kg in the TBI patients compared to 30 gm in most of the normal control studies). These factors confound any comparisons that might be made. The improvement in L-arginine reactivity over time would support the CBF findings from previous studies where vascular function was impaired initially. Nevertheless, with controls for the specific methods that were used in these TBI patients the conclusions might be different.

The study by Okamoto et al.³² also emphasizes the transient nature of the response of the cerebral vessels to L-arginine, and how important the timing of the L-arginine administration and of the measurements of flow velocity is. The convention used in both the control studies

and in the current TBI study was to measure flow velocity just before and at the end of the L-arginine administration. Nevertheless, small differences in timing of the measurements could potentially influence the results.

Although the measurement of FV in the various intracranial vessels is sometimes thought of as regional information, it does not give the high resolution regional CBF information that an imaging technique would provide. CBF is heterogeneous after severe TBI and the FV information represents an average of brain tissue with varying degrees of injury severity and probably varying ability to respond to vasodilators. While there were trends for a more impaired response to L-arginine in the hemisphere with the most severe injury using these dynamic testing methods, such findings might have been clearer with high resolution regional CBF information. Measurement of regional CBF would be important to consider for future studies.

Since CBF does improve with administration of L-arginine after TBI, use of this as a more chronic treatment of a reduced CBF might be considered. The effect of a single bolus of L-arginine on CBF in normal subjects is quite transient.³² Experimental studies using the cortical impact injury model suggest that L-arginine infusion may improve CBF when given very early after injury, but that the effect does not persist even to 24 hr post-injury when given as a continuous infusion.⁴¹ In addition, there is some potential that L-arginine administration after the acute post-injury period could worsen neurological injury by increasing nitric oxide produced by inducible nitric oxide synthase.⁴² Some adverse effects have also been observed with more chronic administration of L-arginine in other disorders. In a large clinical trial of chronic administration of L-arginine in patients with acute myocardial infarction, the study was terminated early because of a higher mortality rate in the L-arginine treated group.⁴³ When chronic administration of L-arginine was used to treat intermittent claudication due to peripheral arterial disease, functional improvement over 6 months of treatment was significantly less in those treated with L-arginine.⁴⁴ Development of tolerance to L-arginine with chronic administration was hypothesized as one explanation for these findings.

Nevertheless, the present studies do suggest that other agents directed at cerebrovascular endothelial dysfunction might be useful in TBI patients. For example, treatment with statins such as atorvastatin have been shown to improve endothelial dysfunction in other disorders.^{23,25} Future studies are needed to determine if such treatments would reduce the cerebrovascular abnormalities that occur after TBI.

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Table 1

Demographics characteristics of 51 patients with severe TBI

	Mean $\pm$ SD or Number (%)	Range
Age (yrs)	35 $\pm$ 14	18 – 64
Gender		
Male	39 (76.5 %)	
Female	12 (23.5 %)	
GCS in ER	6.4 $\pm$ 3.3	3 – 15
AIS score	32 $\pm$ 9	25 – 59
Prehospital hypoxia		
No	43 (84.3%)	
Yes	8 (15.7%)	
Prehospital hypotension		
No	45 (88.2%)	
Yes	6 (11.7%)	
ER CT scan code		
Diffuse injury 1 or 2	20 (39.7%)	
Diffuse injury 3 or 4	7 (13.2%)	
Mass lesion	22 (47.1%)	
Glasgow Outcome Scale		
Good recovery/moderate disability	11 (21.6%)	
Severe disability/vegetative	28 (54.9%)	
Dead	12 (23.5%)	

Abbreviations: GCS = Glasgow Coma Score

AIS = abbreviated Injury Scale

ER = emergency room

SD = standard deviation

CT = computerized tomograph

Table 2

Pressure and oxygenation variables pre- and post L-arginine administration at 12 and 48 hours post-injury.

Variable	12 Hr Post-injury		48 Hr Post-injury		P Value			
	Pre-LA mean (SD)	Post-LA mean (SD)	Pre-LA mean (SD)	Post-LA mean (SD)	Day	L-Arg	Day x L-Arg	Day x L-Arg x Age
ICP	17.8 (9.7)	17.8 (19.1)	17.7 (8.7)	17.7 (7.4)	0.7713	0.7390	0.7779	0.7744
MAP	90.4 (13.3)	90.3 (13.4)	95.6 (12.90) *	93.6 (13.4)	0.0225	0.7758	0.9919	0.7735
ETCO ₂	36.8 (5.8)	36.7 (5.3)	36.1 (5.9)	37.6 (5.4)	0.0932	0.7945	0.6085	0.1482
pCO ₂	40.1 (6.1)	40.2 (5.5)	39.3 (5.4)	39.8 (4.1)	0.2274	0.6103	0.6233	0.2229
SjvO ₂	73.6 (10.9)	73.7 (10.1)	73.2 (10.4)	74.7 (10.0)	0.9535	0.8136	0.7254	0.9067
PbtO ₂	24.5 (18.3)	22.9 (19.6)	22.0 (14.9)	24.0 (18.3)	0.99	0.8036	0.4106	0.5430

* = pre-L-arginine value at 48hr is different from pre-L-arginine value at 12hr (p<.05)

Abbreviations: LA = L-arginine infusion
L-Arg = effect of L-arginine administration
ICP = intracranial pressure
MAP = mean arterial pressure
ETCO₂ = end-tidal carbon dioxide
pCO₂ = arterial carbon dioxide pressure
SjvO₂ = jugular venous oxygen saturation
PbtO₂ = brain tissue pO₂

Table 3

Cerebral hemodynamics pre- and post L-arginine administration at 12 and 48 hours post-injury (the “Worst” side is the hemisphere with the most severe traumatic injury).

Variable: Side	12 hr Post-injury		48 hr Post-injury		P value				
	Pre-LA mean (SD)	Post-LA mean (SD)	Pre-LA mean (SD)	Post-LA mean (SD)	Day	L-Arg	Day x L-Arg	Day x L-Arg x Injury side	Other Factor
ICA-Fvol: Worst	184 (70)	189 (59)	181 (51)	210 (65) [†]	0.1559	0.0190	0.0045	0.7247	
Best	185 (58)	195 (54)	175 (49)	214 (75) [†]					
ICA-FV: Worst	57 (15)	61 (17)	72 (19) *	74 (20)	<0.0001	0.0968	0.6725	0.7641	Age 0.0456
Best	59 (17)	61 (18)	72 (20) *	74 (19)					
ACA-FV: Worst	50 (15)	55 (15)	60 (19) *	64 (16)	<0.0001	0.0029	0.5667	0.6599	
Best	50 (15)	54 (16)	63 (21) *	69 (22)					
MCA-FV: Worst	69 (28)	72 (25)	91 (55) *	93 (27)	<0.0001	0.1886	0.9722	0.5384	
Best	70 (21)	73 (25)	87 (25) *	94 (26)					
PCA-FV: Worst	53 (16)	57 (19)	69 (22) *	72 (23)	<0.0001	0.0597	0.8388	0.6763	
Best	53 (15)	57 (18)	71 (23) *	72 (26)					
ARI: Worst	2.18 (1.37)	2.45(1.94)	1.82 (1.24)	2.04 (1.78)	0.1204	0.0738	0.8783	0.8175	Age 0.0414
Best	2.01 (1.44)	2.14 (1.63)	1.74 (1.43)	1.98 (1.62)					
THRR: Worst	1.13 (0.15)	1.14 (0.15)	1.13 (0.13)	1.13 (0.11)	0.8057	0.1713	0.5540	0.6124	
Best	1.19 (0.14)	1.16 (0.17)	1.16 (0.17)	1.12 (0.12)					
CO₂R: Worst	2.2 (1.5)	3.0 (1.8)	2.5 (1.5)	3.3 (2.1)	0.1520	0.0002	0.1595	0.1880	
Best	2.1 (1.3)	3.4 (2.1)	2.4 (1.8)	2.9 (1.9)					

* pre-L-arginine value at 48hr is different from pre-L-arginine value at 12hr (p<.05)

[†] change with L-arginine infusion at 48hr is different from change with L-arginine infusion at 12hr (p<.05)

Abbreviations: LA = L-arginine infusion
L-Arg: effect = of L-arginine administration

ACA = anterior cerebral artery
MCA = middle cerebral artery
PCA = posterior cerebral artery
F Vol = flow volume
FV = flow velocity
ARI = autoregulation index
THRR = transient hyperemic response ratio
CO₂R = carbon dioxide reactivity

Table 4

Nitrate/nitrite levels in cerebrospinal fluid and serum

Variable	12 Hr Post-injury		48 Hr Post-injury		P Value		
	Pre-LA mean (SD)	Post-LA mean (SD)	Pre-LA mean (SD)	Post-LA mean (SD)	Day	L-Arg	Day x L-Arg
CSF NOx	0.82 (0.40)	1.01 (0.61) *	1.09 (0.74)	0.85 (0.51)	0.4696	0.7018	0.0254
Serum NOx	2.9 (2.8)	2.3 (2.9)	2.3 (2.5)	2.2 (1.9)	0.0852	0.4847	0.3795

* = post-L-arginine value of NOx is different from pre-L-arginine value

Abbreviations: CSF = cerebrospinal fluid

LA = L-arginine infusion

L-Arg = effect of L-arginine administration

SD = standard deviation

NOx = nitrate and nitrite concentrations