Journal of Clinical Neuroscience (2003) **10**(2), 195–198
0967-5868/03/$ - see front matter
doi:10.1016/S0967-5868(02)00126-1

Clinical study

Cerebral blood flow and dynamic cerebral autoregulation during ethanol intoxication and hypercapnia

Martin Blaha MD, Rune Aaslid PHD, Colleen M. Douville BA, Reinaldo Correra RVT, David W. Newell MD,

Department of Neurological Surgery, School of Medicine, University of Washington, Seattle, WA, USA

Summary More than one-third of patients diagnosed with head injury are intoxicated with ethanol. Most clinical and animal studies have shown alcohol to have a deleterious impact in the setting of cerebrovascular trauma; however, there are also data showing neuroprotective effects in low ethanol doses. Human studies using imaging modalities suggest that small doses of alcohol produce cerebral vasodilatation and higher doses cerebral vasoconstriction. The aim of this study was to investigate the effect of ethanol intake on dynamic cerebral autoregulation and velocities in the middle cerebral arteries, and compare these changes with the effects of hypercapnia. Dynamic cerebral autoregulation and cerebral blood flow velocities were analysed before and after alcohol intake (1.1 g/kg of body weight) in six adult volunteers. Cerebral blood flow velocities in both middle cerebral arteries were monitored continuously by transcranial Doppler. A value for dynamic cerebral autoregulation was calculated from the rate of increase in middle cerebral artery velocities after a rapid-step decrease in arterial blood pressure. A sudden decrease in blood pressure was achieved by the release of previously inflated large blood pressure cuffs around the subject's thighs. Three volunteers were also tested before alcohol intake with CO_2 challenge (breathing 6% CO_2) during the autoregulation procedure. Blood alcohol level reached 90 mg/dl approximately 60 min after ethanol ingestion. Cerebral blood velocities increased by 8% from baseline for uncorrected end-tidal (et) CO_2 and by 24% for correction to et $CO_2 = 40$. Dynamic cerebral autoregulation measured as an autoregulation index decreased from 4.3 ± 1.3 to 2.9 ± 1.1 ($p = 0.089$), which did not reach statistical significance. During hypercapnic conditions, dynamic cerebral autoregulation dropped from 4 ± 0.8 to 0.9 ± 0.9. In conclusion, mild alcohol intoxication caused cerebral vasodilatation with a subsequent increase in cerebral blood flow of 8–24%. Dynamic cerebral autoregulation was not found to be significantly impaired by ethanol. Hypercapnia almost completely destroys the physiological autoregulatory mechanism. A mild hyper-ventilation to et$CO_2 = 34$–36 may be a compensatory contra-measure for ethanol-induced vasodilatation in the setting of head trauma

Keywords: alcohol, autoregulation, cerebral blood flow, head injury, hypercapnia, transcranial Doppler ultrasonography

INTRODUCTION

Of the 2657 patients admitted with blunt or penetrating trauma from the emergency room in our regional level I trauma center, 47% had a positive blood alcohol level (BAL) and 35.8% were intoxicated (BAL > l00 mg/dl) on admission.[1] In a group of 520 patients diagnosed with brain injury, 36.7% were intoxicated with ethanol.[2] To adequately treat this significant subpopulation of intoxicated head injury patients, animal and clinical studies have previously been conducted to investigate acute and chronic effects of ethanol on cerebral hemodynamics, metabolism, outcome from head trauma, and the risk of associated complications. Most clinical studies have found alcohol intoxication associated with increased mortality and morbidity.[2–4] Interestingly, further stratification of patients has shown that acute intoxication alone did not increase mortality or risk of complication, in contrast to an intoxicated population with evidence of chronic alcohol abuse, which had a twofold increased risk of complications.[5] Three-fourths of acutely intoxicated patients admitted with trauma in our institution had evidence of chronic alcoholism (positive Short Michigan Alcohol Screening Test) and 30% had bio-chemical evidence of chronic alcohol abuse.[1]

The deleterious impact of ethanol intoxication in the setting of head injury has also been demonstrated in animal studies.[6,7] Other data have demonstrated the neuroprotective effect of low doses of ethanol (1–2.5 g/kg), given prior to traumatic brain injury, due to a decreased degree of uncoupling between glucose metabolism and cerebral blood flow.[8]

Human studies on cerebral blood flow suggest that small doses of alcohol produce cerebral vasodilatation and higher doses produce cerebral vasoconstriction.[9–11] Chronic alcoholism was associated with a reduction of cerebral blood flow and cerebral metabolism.[12] Regional changes in cerebral blood flow were studied using the ^{133}Xe inhalation technique or ^{99m}Tc SPECT (single-photon emission computed tomography), and showed a vasodilatory effect in prefrontal and temporal regions.[10,11]

The aim of this study was to investigate the effect of ethanol intake on dynamic cerebral autoregulation and compare these changes with the effects of hypercapnia. A second target was to evaluate the changes in velocities from the middle cerebral arteries and correlate them with changes in cerebral blood flow.

MATERIALS AND METHODS

The study was approved by the University of Washington Human Subject Review Committee. Written informed consent was obtained from each volunteer.

Subjects

Six healthy adult volunteers (five males and one female) with no history of alcohol abuse participated in this study. Their ages were between 27 and 39 years (mean 32.5 ± 4.1) and they described themselves as social drinkers. We advised them to not drink any alcohol for 24 h prior to testing and to avoid caffeine-containing beverages for 6 h prior to the test.

Received 15 February 2002
Accepted 25 April 2002

Correspondence to: Dr Martin Blaha, Neurosurgery Department, Royal Perth Hospital, Box X2213 GPO, Perth, WA 6847, Australia.
Tel.: +61-08-9224-2596; Fax: +61-08-9224-8099;
E-mail: drmartinblaha@yahoo.com

Alcohol source and blood alcohol level measurement

As a source of ethyl alcohol, Wild Turkey whisky, 50% alcohol, was used. Blood alcohol level (BAL) was measured with a breath analyzer (BAC Datametr, National Patent Analytical Systems, OH, USA).

Hemodynamics measurement

A headband was placed onto the subject's head allowing secure attachment of a left and right transducer over the temporal windows. Velocities from both middle cerebral arteries were continuously monitored at a depth providing the best signal (50–54 mm) using TCD equipment (MultidopX, DWL, Sipplingen, Germany). Non-invasive continuous blood pressure and heart rate were recorded with a tonometric sensor (CBM-7000, Colin, San Antonio, TX, USA) placed over the right radial artery and a pneumatic calibration cuff placed on the right upper arm. End-tidal (et) CO_2 concentration was intermittently measured with a CO_2 analyzer (Datex 223, Puritan-Bennett, Tewksbury, MA, USA).

Dynamic cerebral autoregulation

Large blood pressure cuffs were placed around both thighs of the subject. The cuffs were attached to an inflation device (E-20 Rapid cuff inflator, Hokanson, Bellevue, WA, USA) and inflated to 30 mmHg above systolic blood pressure for 3–4 min. The sudden release of these cuffs caused a rapid-step decrease in arterial blood pressure, which remained lowered for approximately 20 s and then gradually returned to baseline values. A drop in arterial blood pressure of more than 15 mmHg was considered to be valid for testing the auto-regulation response. Velocities in both middle cerebral arteries decreased with the blood pressure drop but returned more rapidly to their initial level, depending on autoregulation ability. The software algorithm developed by Aaslid and coworkers[13] compares the rate of return of velocities in the middle cerebral artery to the rate of return of the arterial blood pressure and calculates an autoregulation index (ARI). This ARI has 10 different values, from 0 [no autoregulation, velocity in MCA (Vmca) passively follows changes in arterial blood pressure] to 9 (accentuated autoregulatory response with an almost immediate return of Vmca to baseline despite a still low arterial blood pressure).

Testing protocol

Velocities from both middle cerebral arteries, blood pressure, heart rate and $etCO_2$ were measured on each subject during resting conditions. Dynamic cerebral autoregulation was performed twice and the ARI was calculated as an average from both measurements, from both sides. Subjects then ingested 0.6 g/kg body weight of alcohol during 20 min. Repeat measurement of hemodynamic parameters and BAL was done and subjects received a second dose of alcohol 0.5 g/kg body weight. After this second dose we again measured Vmca, arterial blood pressure, heart rate, $etCO_2$ and BAL and performed autoregulation testing (twice) with subjects under the influence of alcohol. Sixty minutes after the time of the first ingestion hemodynamic parameters and BAL were measured a final time.

Dynamic cerebral autoregulation with CO_2 challenge

Three volunteers were also tested before alcohol intake with CO_2 challenge during an autoregulation response. The special mixture of gas consisting of 6% CO_2, 40% oxygen and a balance of nitrogen was delivered to the subjects through a one-way breathing valve. The subjects were asked to breathe this gas mixture for 3 min before testing autoregulation (cuff deflation). This autoregulation test with CO_2 challenge was also repeated twice and the ARI was calculated as an average from both tests and both sides.

RESULTS

The results of our study are summarized in Table 1. No volunteer had significant side differences in middle cerebral artery velocities, so we averaged these numbers for every subject. Mean velocity in the MCA increased during alcohol ingestion from baseline 63.5 ± 9.7 to 68.5 ± 8.4 cm/s ($p = 0.015$) during alcohol blood levels of 90.3 ± 19.9 mg/dl. This represents a 7.9% increase from baseline values. The $etCO_2$ at the same time dropped from 40.7 ± 2.2 to 36.7 ± 2.6 mmHg. To correct these $etCO_2$ changes for measured velocities, we recalculated all Vmca at et CO_2 level of 40 mmHg. A value of 3.4% change in Vmca per 1 mmHg of $etCO_2$ was used.[14] The corrected mean velocity increased by 76% from 62.0 to 77.3 cm/s ($p = 0.002$). Pulsatility index (PI) was also averaged from both middle cerebral arteries for every subject. Compared to a value of 0.86 ± 0.13 before alcohol ingestion, PI decreased to 0.77 ± 0.16 during the highest blood alcohol level. We did not use any PI correction for $etCO_2$ changes due to a lack of supportive data in the literature.

Mean ARI with a BAL = 0 was 4.5 ± 1.1. A second measurement during alcohol intoxication (BAL = 90.3 ± 19.9) showed decreased ARI to 3.6 ± 1.2. For CO_2 correction we used our data from autoregulation testing with CO_2 challenge, which showed an 8.2% decrease in ARI for every 1 mmHg of $etCO_2$ increase. Recalculated ARI for $etCO_2 = 40$ mmHg was 4.2 before alcohol ingestion and 2.9 with BAL = 90.3 ± 19.9. Neither the uncorrected nor corrected ARI decrease was statistically significant (paired t test, $p = 0.136$ and or 0.078, respectively). When dynamic cerebral autoregulation was tested with CO_2 challenge, ARI decreased from 4 ± 0.75 to 0.9 ± 0.9.

Table 1 Results of ethanol intoxication

	Baseline	20 min	40 min	60 min
Alcohol level (mg/dl)	0	45.4 ± 12.4	87.5 ± 19.4	90.3 ± 19.9
$etCO_2$ (mgHg)	40.7 ± 2.2	38.6 ± 2.7	38.5 ± 1.0	36.7 ± 2.6
Vmca (cm/s)	63.5 ± 9.7/100%	63.8 ± 9.9/100.5%	67.8 ± 11.6/106.8%	68.5 ± 8.4/107.9%
Vmca corrected to $etCO_2 = 40$ mmHg (cm/s)	62.0 ± 7.7/100%	67.0 ± 8.2/108.1%	71.4 ± 11.6/115.1%	77.3 ± 6.4/124.6%
PI	0.86 ± 0.13	0.75 ± 0.22	0.77 ± 0.12	0.77 ± 0.16
HR (beats/min)	63.7 ± 14.4	68 ± 13.6	72.7 ± 16.4	68.3 ± 13.0
SBP (mmHg)	114.7 ± 9.0	119.2 ± 14.1	116.7 ± 17.3	116.3 ± 9.3
DBP (mmHg)	58.8 ± 6.2	67.0 ± 9.1	62.2 ± 10.1	60.7 ± 7.5
ARI/$etCO_2$	4.5 ± 1.1/39.0			3.6 ± 1.2/37.2
ARI correlated to $etCO_2 = 40$ mmHg (cm/s)	4.3 ± 1.3			2.9 ± 1.1

$etCO_2$, end-tidal $etCO_2$; Vmca, velocity in the middle ceretral artery; PI, pulsatility index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARI, autoregulation index.

DISCUSSION

Cerebral blood flow

In our study we used transcranial Doppler to non-invasively assess cerebral hemodynamics. This method does not measure absolute cerebral blood flow but is able to provide reliable data about relative changes in CBF based on the assumption that the MCA diameter does not change and, therefore, changes in middle cerebral artery velocity are directly related to changes in cerebral blood flow. This assumption was confirmed by Newell et al.[15] comparing intraoperative flow in the internal carotid artery versus transcranial velocities in the MCA.

The present study shows increased mean velocities in the middle cerebral arteries from 63.5 ± 9.7 to 68.5 ± 8.4 cm/s (+7.9%). The paired Student's *t* test was used to analyze these data and showed statistical significance ($p = 0.015$). Cerebral blood flow and Vmca are very sensitive to changes in CO_2 levels. Markwalder et al.[14] showed that for every 1 mm increase (decrease) in CO_2, Vmca increased (decreased) by 3.4%. Because of unequal values of $etCO_2$ during our Vmca measurements, we corrected all measured values to an $etCO_2 = 40$ mmHg using an index of 3.4%/l mmHg CO_2. The corrected Vmca values showed a steady increase from 62.0 ± 7.7 to 77.3 ± 6.4 cm/s (+24.6%). This difference was statistically significant ($p = 0.02$). This increase in middle cerebral arteries is caused by vasodilatation in the peripheral cerebral vessels caused by alcohol and results in increased cerebral blood flow during mild alcohol intoxication. The index for CO_2 correction was calculated for sudden changes in CO_2 with subsequent immediate measurement of changes in Vmca. In our study CO_2 changes were slow during the 60 min interval and vascular tone may have had time to adapt to a new CO_2 level. There are no data to precisely adjust this time factor. We can say that mild alcohol intoxication increased cerebral blood flow by 8–24% as a function of increased velocities in both MCAs. This finding is consistent with studies using ^{133}Xe or ^{99m}Tc SPECT to measure CBF which showed a 12–14% increase compared to baseline.[10,11] These CBF changes represent cerebral vasodilatation with BAL around 90 mg/dl. As previously mentioned, there may be a small amount of time adaptation for changes in vascular tone, and it is important to understand that if our volunteers were intubated and ventilated to $etCO_2 = 40$ mmHg, the cerebral blood flow would be 24.4% higher compared to their sober status. If patients present with increased intracranial pressure, alcohol related increases in CBF could be one of the causative factors of such an increase. As a treatment strategy, it is essential to avoid hypercapnia; and if ICP needs to be targeted, mild hyperventilation to $etCO_2 = 3436$ mmHg can be used. Hypocapnia decreases CBF by approximately 13.6–20.4% and compensates for the vasodilatative effect of alcohol. Further data are needed to better determine the time adjustment of the cerebral vasculature to changes in CO_2 and to identify changes in CBF relative to blood alcohol level.

Autoregulation

Dynamic cerebral autoregulation was assessed with the method developed by Aaslid et al.[16,17] using a rapid-step decrease in arterial blood pressure after the release of large blood pressure cuffs placed around the thighs of the subjects. The drop and consequent return of blood pressure back to baseline is compared with velocities in middle cerebral arteries, and the ability of the cerebral vasculature to compensate for blood pressure fluctuations is calculated as an ARI. It was previously demonstrated that volatile anesthetic agents such as isoflurane or desflurane disturbed autoregulatory responses.[18] Studies on patients with severe head trauma [Glasgow Coma Scale $(GCS) \leqslant 8$] showed significant impairment of autoregulation as a result of decreased vascular tone.[19] In a group of patients with minor head injury (GCS 13–15) there was a subgroup of patients with impaired autoregulatory response.[20] The statistically significant cutoff between ''intact'' and impaired autoregulation was found to be 2.5. The mean ARI before ingestion of alcohol was, in our study, 4.5 ± 1.1 and decreased to 3.6 ± 1.2 when the BAL reached 90.3 mg/dl. Because of unequal $etCO_2$ 39 and 37.2 mmHg, respectively, we corrected the original values to $etCO_2$ equal to 40 mmHg. For this correction we used our data from testing dynamic cerebral autoregulation during CO_2 challenge, which showed an 8.24% decrease in ARI per 1 mmHg of CO_2 increase. We are aware that the index for this correction is based on a small number of subjects and gave us only a rough estimation for correction. Our target was to find whether this correction brought any significant difference compared to uncorrected values. The paired Student's *t* test was performed and did not show statistical significance between baseline and alcohol values, for either uncorrected or corrected ARI ($p = 0.136$ and 0.078). On the other side, dynamic cerebral autoregulation tests with CO_2 challenge showed significant impairment under hypercapnic conditions as previously described by Aaslid et al.[16] The ARI decreased from baseline values of 4 ± 0.8 to 0.9 ± 0.9 as a result of decreased vascular tone in the cerebral peripheral vasculature.

Our results showed only mild, statistically not significant, decreases in the dynamic autoregulation response based on mild alcohol-related vasodilatation. As the most important regulator of this physiological principle, the $etCO_2$ ($PaCO_2$) was identified. During hypercapnia-related vasodilatation, the cerebral vasculature does not have an adequate mechanism to compensate for a sudden drop in blood pressure, which results in severe autoregulation impairment. Conversely, hyperventilation can temporarily improve the autoregulatory response as a result of an increase in vascular tone.[19] Severe head-injured patients and approximately one-third of patients following minor head injury demonstrate impairment of their autoregulation due to trauma-induced decreases in cerebral vascular tone. The most efficient treatment strategy is to protect our patients from hypoventilation, which causes rising $PaCO_2$ and further impairment of the autoregulatory response.

ACKNOWLEDGEMENTS

We thank Washington State Police, particularly Sergeant Rod G. Gullberg and Trooper Brian I. Bowers, for their help with BAL measurement and their support. We also thank all the volunteers

REFERENCES

1. Rivara FP, Jurkovich GJ, Gurney JG et al. The magnitude of acute and chronic alcohol abuse in trauma patients. Arch Surg 1993; 128: 907–913.
2. Gurney JG, Rivara FP, Mueller BA, Newell DW, Copass MK, Jurkovich GJ. The effects of alcohol intoxication on the initial treatment and hospital course of patients with acute brain injury. J Trauma 1992; 33: 709–713.
3. Pories SE, Gamelli RL, Vacek P, Goodwin G, Shinozaki T, Harris F. Intoxication and injury. J Trauma 1992; 32: 60–64.
4. Zink BJ, Maio RF, Chen B. Alcohol, central nervous system injury, and time to death in fatal motor vehicle crashes. Alcohol Clin Exp Res 1996; 20: 1518–1522.
5. Jurkovich GJ, Rivara FP, Gumey JG et al. The effect of acute alcohol intoxication and chronic alcohol abuse on outcome from trauma. JAMA 1993; 7(270): 93–94.
6. Zink BJ, Sheinberg MA, Wang X et al. Acute ethanol intoxication in a model of traumatic brain injury with hemorrhagic shock: effects on early physiological response. J Neurosurg 1998; 89: 983–990.

7. Zink BJ, Walsh RF, Feustel PJ. Effects of ethanol in traumatic brain injury. J Neurotrauma 1993; 10: 275–286.
8. Kelly DF, Kozlowski DA, Haddad E, Echiverri A, Hovda DA, Lee SM. Ethanol reduces metabolic uncoupling following experimental head injury. Neurotrauma 2000; 17: 261–272.
9. Mathew RJ, Wilson WH. Substance abuse and cerebral blood flow. Am J Psychiatry 1991; 148: 292–305.
10. Sano M, Wendt PE, Wirsen A, Stenberg G, Risberg J, Ingvar DH. Acute effects of alcohol on regional cerebral blood flow in man. J Stud Alcohol 1993; May: 369–376.
11. Tiihonen J, Kuikka J, Hakola P et al. Acute ethanol-induced changes in cerebral blood flow. Am J Psychiatry 1994; 151: 1505–1508.
12. Berglund M, Hagstadius S, Risberg J, Johanson TM, Bliding A, Mubrin Z. Normalization of regional cerebral blood flow in alcoholics during the first 7 weeks of abstinence. Acta Psychiatr Scand 1987; 75: 202–208.
13. Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. Stroke 1995; 26: 1014–1019.
14. Markwalder TM, Grolimund P, Seiler RW, Roth F, Aaslid R. Dependency of blood flow velocity in the middle cerebral artery on end-tidal carbon dioxide partial pressure – a transcranial ultrasound Doppler study. J Cereb Blood Flow Metab 1984; 4: 368–372.
15. Newell DW, Aaslid R, Lam A, Mayberg TS, Winn HR. Comparison of flow and velocity during dynamic autoregulation testing in humans. Stroke 1994; 25: 793–797.
16. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke 1989; 20: 45–52.
17. Aaslid R, Newell DW, Stooss R, Sorteberg W, Lindegaard KF. Assessment of cerebral autoregulation dynamics from simultaneous arterial and venous transcranial Doppler recordings in humans. Stroke 1991; 22: 1148–1154.
18. Strebel S, Lam AM, Malta B, Mayberg TS, Aaslid R, Newell DW. Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. Anesthesiology 1995; 83: 66–76.
19. Newell DW, Weber JP, Watson R, Aaslid R, Winn HR. Effect of transient moderate hyperventilation on dynamic cerebral autoregulation after severe head injury. Neurosurgery 1996; 39: 35–44.
20. Junger EC, Newell DW, Grant GA et al. Cerebral autoregulation following minor head injury. J Neurosurg 1997; 86: 425–432.

