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Cerebral Metabolism and EEG During Combination of Hypocapnia and Isoflurane-induced Hypotension in Dogs

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Isoflurane (ISF)-induced hypotension causes equal reductions of cerebral blood flow (CBF) and the cerebral metabolic rate for oxygen (CMR_{O_2}) so that no disturbance of cerebral energy stores or metabolites occurs. While hypocapnia during ISF-induced hypotension causes a further reduction of CBF, the effects on cerebral energy stores and metabolites produced by combining hypocapnia with ISF-induced hypotension are not known. This study examined the effect of hypocapnia (Pa_{CO_2} = 20 mmHg) on CMR_{O_2}, the electroencephalogram (EEG), and levels of adenine nucleotides, phosphocreatine, lactate, pyruvate, and glucose in brain tissue in 12 dogs during ISF-induced hypotension. All dogs were examined at: 1) normocapnia with normotension; 2) hypocapnia with normotension; 3) hypocapnia combined with ISF-induced hypotension to cerebral perfusion pressures of 60, 50, and 40 mmHg; and 4) restoration of normocapnia with normotension. In six dogs CMR_{O_2} was determined, and the EEG was evaluated using compressed spectral analysis. In the other six dogs brain tissue metabolites were determined. Hypocapnia combined with ISF-induced hypotension (all levels) caused a decrease of the power of the beta-2 spectra, an increase of the power of the alpha and beta-1 spectra, but no change in total power of the EEG. There was no change in cerebral energy stores or brain tissue metabolites. CMR_{O_2} was reduced by approximately 27%. Thirty mintues after restoration of normocapnia with normotension, cerebral metabolites remained unchanged and CMR_{O_2}, and the power of the alpha, beta-1, and beta-2 spectra of the EEG returned to control values. These results suggest no adverse effect on cerebral metabolism or function during hypocapnia combined with ISF-induced hypotension. (Key words: Anesthetic techniques: hypotension, induced; isoflurane. Anesthetics, volatile: isoflurane. Brain: electroencephalography; metabolism. Carbon dioxide: hypocapnia. Vasodilator agents.)

NEWBERG *ET AL.* recently examined the effect of isoflurane (ISF)-induced hypotension on cerebral blood flow (CBF) and metabolism.[1] They reported that in normocapnic dogs reduction of cerebral perfusion pressure (CPP) to as low as 22 mmHg caused significant reductions of CBF and the cerebral metabolic rate for oxygen (CMR_{O_2}) that were of similar magnitude. Cerebral energy stores and metabolites were maintained at normal values. In contrast, earlier work from the same laboratory reported that in normocapnic dogs, reduction of CPP to 40 or 30 mmHg with trimethaphan (TMP) or to 30 mmHg with sodium nitroprusside (SNP) or halothane caused a reduction of CBF that exceeded the reduction of CMR_{O_2}.[2] Severe disturbances of cerebral energy stores and metabolites resulted. It was concluded that during normocapnia ISF may offer advantages over the other hypotensive techniques.

However, when elective, controlled, hypotension is used for neurologic surgery, hypotension frequently is induced while patients are hypocapnic. Two recent studies raise the concern that hypocapnia may oppose the potentially advantageous cerebral effects of ISF during ISF-induced hypotension. Drummond *et al.* reported that ISF enhances the responsiveness of the cerebral vasculature to Pa_{CO_2} and that hypocapnia during ISF anesthesia causes cerebral vasoconstriction, reducing CBF to values significantly lower than those with hypocapnia during halothane anesthesia or sedation with nitrous oxide.[3] Artru reported that hypocapnia also causes cerebral vasoconstriction during ISF-induced hypotension.[4] The results of Drummond *et al.*[3] and Artru[4] suggest that combining hypocapnia with ISF-induced hypotension may cause a reduction of CBF that exceeds the reduction of CMR_{O_2} so that oxygen and substrate delivery to brain become inadequate, leading to a deterioration of cerebral energy stores and metabolites.

The present study was designed to examine cerebral energy stores and metabolites and the electroencephalogram (EEG) during hypocapnia combined with ISF-induced hypotension. CPP values of 60, 50, and 40 mmHg were examined. These values were selected because they encompass the range commonly employed for elective hypotension in clinical practice.[5] The goals of the study were to determine whether cerebral energy stores and metabolites and the EEG are disturbed during hypocapnia combined with ISF-induced hypotension and, if so, how the magnitude of the disturbances compares with the magnitude of the cerebral metabolic and EEG disturbances previously reported for hypocapnia plus hypotension induced with SNP, TMP, or nitroglycerin (NTG).[6,7]

Methods

Following approval from the animal care committee, 12 unmedicated mongrel dogs, weighing 12.4–22.7 kg, were anesthetized with ISF (>1.8%, inspired) and nitrous oxide (66%) in O_2. The trachea was intubated, and ventilation was controlled with a Harvard® pump (Harvard Apparatus Co., Millis, MA) and adjusted along with the inspired O_2 concentration to maintain initial blood-gas tensions (Radiometer® BMS3 MK 2 electrodes, [Radiometer A/S, Copenhagen, Denmark]) at Pa_{O_2} > 120

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mmHg and Pa_{CO_2} = 40 ± 1 mmHg (mean ± SEM). With the animal in the lateral position, a urinary catheter was placed and both femoral veins were cannulated for fluid and drug administration, and reinfusion of blood collected from a sagittal sinus cannula (see following). Intravenous infusion of succinylcholine 50–120 mg/h maintained muscle relaxation. The right femoral artery was cannulated for arterial blood sampling for blood-gas analyses, and for continuous monitoring of systemic arterial pressure and heart rate. Mean arterial pressure (MAP) was determined by electronic integration. Expired CO_2 was continuously monitored via a Beckman LB-2® medical gas analyzer (Beckman Instruments, Inc., Fullerton, CA). Temperature was monitored by a nasopharyngeal thermistor probe and maintained at 37.0 ± 0.5° C by heat lamps or ice packs. Depletion of vascular volume was minimized by continuous infusion of saline 4–6 $ml \cdot kg^{-1} \cdot h^{-1}$. The animal was then turned to the prone position and the head slightly elevated and fixed in a stereotaxic frame. The strain gauge used to measure systemic arterial pressure was positioned 15 cm above heart level. The zero reference for the strain gauge was set at the level of the top of the dog's head.

Measurement of CBF, CMR_{O_2} and EEG

Six of the 12 dogs were surgically prepared for measurement of CBF and CMR_{O_2} and recording of the EEG. The method of measurement of CBF was previously described in detail and is summarized here.[8] The sagittal sinus was exposed *via* craniectomy and, following systemic intravenous infusion of heparin 8,000 units, the posterior sagittal sinus was incised and a snug-fitting, tapered nylon catheter (2 mm internal diameter) was passed anteriorly 2–4 mm. The sinus was packed with strips of Surgicel® (Johnson and Johnson Products, New Brunswick, NJ) through another incision just posterior to the catheter, assuring total diversion of sagittal sinus flow through the catheter. The distal tip of the catheter was placed at the level of the base of the skull, and flow from the catheter was collected in a reservoir and returned by a roller pump to the femoral vein. The reservoir and pump initially were primed with saline and the fluid level in the reservoir was maintained at 100 ml ± 2 ml/kg. Sagittal sinus blood samples for measurement of oxygen tension were drawn into syringes through a side-arm at the distal tip of the sagittal sinus outflow catheter by gentle aspiration. At each experimental condition CBF, expressed as ml/min, was determined by 3–5 timed collections of outflow from the sagittal sinus catheter. Along with each determination of CBF, CMR_{O_2}, expressed as ml/min, was determined as the product of CBF and the arterial–sagittal sinus blood O_2 content difference ($Ca_{O_2} - Cv_{O_2}$). Arterial and sagittal sinus blood O_2 contents were determined from measurements of oxygen tension, hemoglobin concentration (IL 282 CO-Oximeter® Instrumentation Laboratory, Inc., Lexington, MA), and O_2 saturation[9,10] using 1.36 ml/g as the O_2 carrying capacity of hemoglobin[11] as reported previously.[6] Conversion of CBF values from ml/min to $ml \cdot min^{-1} \cdot 100\ g^{-1}$ was based on brain weight and the portion of brain that contributed to sagittal sinus flow, namely 48%, as reported previously.[12,13] Three to five CBF values and 3–5 CMR_{O_2} values were averaged to provide representative mean CBF and CMR_{O_2} values for each experimental condition. Brains were excised and weighed after the final experimental condition.

Also, at each experimental condition concentrations of lactate, pyruvate, and glucose in arterial blood samples were determined using standard techniques, and the lactate–pyruvate (L/P) ratio was calculated. The EEG was recorded using bilateral frontoparietal electrodes and a Beckman Acutrace® polygraph (Beckman Instruments, Inc., Fullerton, CA) with a bandpass of 0.3 to 75 Hz. Electrodes were adjusted to maintain impedances between electrode pairs at <3 KΩ. Computer (Digital Equipment Corp. MINC-23®, Digital Equipment Corp., Marlboro, MA) analysis of the EEG was performed using a Compressed Spectral Array (CSA) program, which averaged the EEG power spectra of four epochs (1 epoch = 4 s) every 30 s.[14,15] For each experimental condition the EEG power spectra for that time period were averaged to provide mean power in the standard frequency bins: delta (δ, 1–4 Hz), theta (θ, 4–8 Hz), alpha (α, 8–14 Hz), beta 1 (β_1, 14–20 Hz), and beta 2 (β_2, 20–32 Hz). For all experimental conditions the mean power of each frequency bin was normalized to the mean power in that frequency bin during the first experimental condition. Total EEG power was defined as the sum of the mean power values of each frequency bin. For all experimental conditions total EEG power was normalized to total EEG power during the first experimental condition.

After completion of the surgical preparation the expired concentration of ISF was decreased to 0.33% (end-expired concentration determined by gas chromatography, nitrous oxide continued). After stable measurements of cerebral and systemic variables were obtained (at least 25 min later), CBF, CMR_{O_2}, EEG, and systemic variables were determined at each of six experimental conditions (table 1). The duration of each condition was 30 min, with 25 min allowed to achieve and maintain the desired condition and 5 min used to determine all cerebral and systemic variables except the EEG, which was recorded during the final 10 min of each condition. Hyperventilation was used to decrease Pa_{CO_2}. The desired level of hypotension was achieved by increasing the concentration of ISF. The dura was opened throughout the study so that CPP equalled MAP measured at head level. End-expired ISF concentrations were determined at each ex-

TABLE 1. Sequence of Experimental Conditions

Condition	Pa_{CO_2} (mmHg)	CPP (mmHg)
1	40	Normal*
2	20	Normal*
3	20	60
4	20	50
5	20	40
6	40	Normal*

CPP = cerebral perfusion pressure.
* Actual values are noted in Tables 4, 5.

perimental condition. In all six dogs, after values were determined at condition 6, a brain biopsy specimen was obtained for determination of brain tissue metabolites (see following).

MEASUREMENT OF BRAIN TISSUE METABOLITES

The other six of 12 dogs were surgically prepared for measurement of brain tissue concentrations of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), phosphocreatine (PCr), lactate, pyruvate, and glucose. A craniectomy was performed and the dura overlying the cerebral hemispheres was excised. At each experimental condition brain tissue samples were obtained using a suction technique that deposits a tissue sample (200–400 mg) into liquid nitrogen within 1 s.[16] At least 2 cm of brain was left between biopsy sites to prevent tissue reaction at early biopsy sites from disturbing metabolite values at later biopsy sites.[16] Each tissue sample was stored at −76° C for no longer than 24 h, then extracted and analyzed using enzymatic fluorometric techniques.[17] From these values the sum of adenine nucleotides (ΣAd = [ATP] + [ADP] + [AMP]) and the L/P ratio were determined. The energy charge (EC) of the adenine nucleotide pool was calculated as: EC = ([ATP] + 0.5 [ADP])/ΣAd.[18,19] Also determined at each experimental condition were the concentrations of lactate, pyruvate, and glucose in arterial blood, and the arterial blood L/P ratio was calculated.

After completion of the surgical preparation the expired concentration of ISF was decreased to 0.33%. After stable measurements of systemic variables were obtained (at least 25 min later), brain tissue was sampled and systemic variables were determined at the same experimental conditions as for the studies of CMR_{O_2} and EEG, allowing 30 min at each condition. Hyperventilation was used to decrease Pa_{CO_2}, and the desired level of hypotension was achieved by increasing the concentration of ISF.

Cerebral and systemic variables were compared between conditions using analysis of variance for repeated measures.[20] Values at conditions 2–6 were compared with values at condition 1. Values at conditions 3–5 also were compared with values at condition 2. Where the calculated F value exceeded the critical value for 0.05 probability, the Student-Newman-Keuls' test was employed to make comparisons within groups.[21] A P value of less than 0.05 was considered significant.

Results

During normotension, reducing Pa_{CO_2} caused a significant decrease of CBF and sagittal sinus oxygen tension (PSS_{O_2}) (table 2). The power of the β_2 spectrum of the EEG (fig. 1), $Ca_{O_2} - Cv_{O_2}$, and brain tissue lactate and pyruvate (table 3) all increased, though the brain tissue L/P ratio was not significantly altered. Systemic variables also were affected by hypocapnia (tables 4 and 5). Arterial blood pH, lactate, and pyruvate increased, while arterial blood bicarbonate decreased.

TABLE 2. Cerebral Values During Measurement of CBF, CMR_{O_2}, and EEG (mean ± SEM) (n = 6)

	Normal CPP Pa_{CO_2} = 40 mmHg	Normal CPP Pa_{CO_2} = 20 mmHg	CPP = 60 mmHg Pa_{CO_2} = 20 mmHg	CPP = 50 mmHg Pa_{CO_2} = 20 mmHg	CPP = 40 mmHg Pa_{CO_2} = 20 mmHg	Normal CPP Pa_{CO_2} = 40 mmHg
CBF (ml · min^{-1} · 100 g^{-1})	95 ± 11	51 ± 6*	45 ± 4*	41 ± 4*	37 ± 5*†	81 ± 7*
$Ca_{O_2} - Cv_{O_2}$ (ml/dl)	3.6 ± 1.0	7.5 ± 1.6*	6.2 ± 1.0*	6.8 ± 1.2*	7.3 ± 1.6*	4.2 ± 1.1
CMR_{O_2} (ml · min^{-1} · 100 g^{-1})	3.52 ± 0.37	3.72 ± 0.34	2.69 ± 0.19*†	2.63 ± 0.13*†	2.59 ± 0.16*†	3.38 ± 0.35
PSS_{O_2} (mmHg)	57 ± 4	35 ± 3*	36 ± 2*	34 ± 2*	32 ± 3*	48 ± 3
EEG power (per cent)‡						
Delta	100	92 ± 19	100 ± 18	84 ± 14	99 ± 29	102 ± 29
Theta	100	108 ± 12	134 ± 31	126 ± 29	128 ± 32	128 ± 33
Alpha	100	105 ± 8	159 ± 19*†	167 ± 28*†	188 ± 33*†	102 ± 17
Beta 1	100	131 ± 15	196 ± 33*†	193 ± 33*†	156 ± 32	104 ± 11
Beta 2	100	147 ± 16*	83 ± 15†	74 ± 9*†	76 ± 9*†	91 ± 10*
Total	100	113 ± 15	122 ± 24	122 ± 25	119 ± 25	104 ± 20

See text for abbreviations.
PSS_{O_2} = oxygen tension of sagittal sinus blood.
* Significant difference from values at normal CPP and Pa_{CO_2} = 40 mmHg, $P < 0.05$.
† Significant difference from values at normal CPP and Pa_{CO_2} = 20 mmHg, $P < 0.05$.
‡ Per cent relative to EEG power values at normal CPP and Pa_{CO_2} = 40 mmHg.

Inducing hypotension with ISF during hypocapnia caused no deterioration of cerebral metabolites or the EEG. Specifically, there was no reduction of brain tissue PCr, brain tissue glucose, the EC, or total EEG power, and no increase of brain tissue lactate or the brain tissue L/P ratio. Hypotension (CPP $\leq$ 60 mmHg) caused by high concentrations of ISF (1.92–2.67%, end-expired concentrations) was accompanied by a decrease of CMR_{O_2} (by 24–27%) and a shift of EEG power to lower frequency. At CPP $\leq$ 60 mmHg the power of the β_2 spectrum decreased while the power of the α and β_1 spectra increased. At CPP = 40 mmHg CBF was reduced compared with values caused by hypocapnia with normal CPP. Systemically, hypotension plus hypocapnia was accompanied by a decrease of arterial blood bicarbonate and glucose, a variable decrease of arterial blood pyruvate, and an increase of arterial blood lactate.

With restoration of normal CPP and Pa_{CO_2}, cerebral metabolites and the EEG were not significantly changed compared with initial values. The only exception was brain tissue pyruvate, which was reduced compared with initial values at normal CPP and Pa_{CO_2}. However, the brain tissue L/P ratio was not significantly different from initial values. Brain biopsy samples taken at the end of the studies from animals surgically prepared for determination of CMR_{O_2} and EEG were not significantly different from those taken at the end of the study from animals surgically prepared for brain biopsy sampling (table 6). Systemically, final values for the arterial blood L/P ratio were increased compared with initial values, and there was a variable decrease in arterial blood pyruvate values.

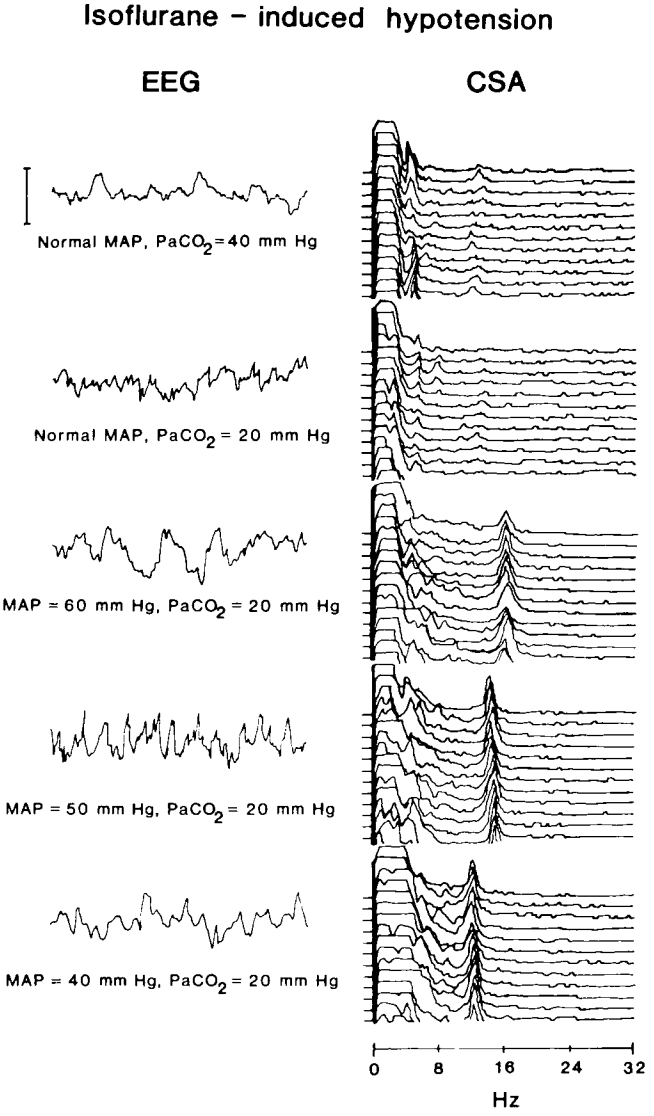

FIG. 1. EEG and CSA from one dog are shown at normal MAP with and without hypocapnia, and at isoflurane-induced hypotension combined with hypocapnia. Each EEG trace represents 2 s of EEG activity recorded at 30 mm/s. The calibration mark denotes 50 μv. CSA spectra are displayed at 30-s intervals.

Discussion

The present results suggest no adverse effect on cerebral metabolism and function during hypocapnia plus ISF-induced hypotension to CPP as low as 40 mmHg for 30 min. Cerebral energy stores and metabolites were unchanged, and there was no reduction of total EEG power, but simply a shift of EEG activity from the β_2 spectrum to the α and β_1 spectra. Previous studies reported that mild hypoxia or ischemia causes an increase of brain tissue lactate and the L/P ratio, and a decrease of brain tissue PCr.[2,22–29] More severe hypoxia or ischemia causes a decrease of the EC and brain tissue glucose and, ultimately, a decrease of CMR_{O_2}. Regarding the EEG, mild hypoxia or ischemia causes a decrease of total EEG power characterized by a decrease of α activity with or without a decrease of β activity.[30–35] More severe ischemia or hypoxia causes a decrease of all high-frequency activity and, ultimately, complete EEG suppression. That these patterns of metabolic and EEG changes indicative of hypoxia or ischemia were not observed in the present study suggests that cerebral integrity and function are preserved during combination of hypocapnia and ISF-induced hypotension.

One explanation for preservation of normal metabolites may be the reduction of CMR_{O_2} caused by the high concentrations of ISF necessary to induce hypotension. In the present study CMR_{O_2} decreased by 24–27% when the concentration of ISF was increased to 1.92–2.67% (end-expired concentrations). By reducing CMR_{O_2} at a time when CBF also was reduced, ISF tended to preserve the ratio of oxygen delivery to oxygen demand.

TABLE 3. Cerebral Values During Measurement of Brain Tissue Metabolites (mean ± SEM) (n = 6)

	Normal CPP Pa_{CO_2} = 40 mmHg	Normal CPP Pa_{CO_2} = 20 mmHg	CPP = 60 mmHg Pa_{CO_2} = 20 mmHg	CPP = 50 mmHg Pa_{CO_2} = 20 mmHg	CPP = 40 mmHg Pa_{CO_2} = 20 mmHg	Normal CPP Pa_{CO_2} = 40 mmHg
PCr (μmol/g)	3.94 ± 0.48	5.07 ± 0.43	4.20 ± 0.50	5.94 ± 0.59	5.32 ± 0.39	5.55 ± 0.49
ATP (μmol/g)	2.03 ± 0.11	2.01 ± 0.12	1.87 ± 0.14	1.85 ± 0.07	2.19 ± 0.08	2.05 ± 0.12
ADP (μmol/g)	0.36 ± 0.05	0.35 ± 0.05	0.32 ± 0.02	0.33 ± 0.03	0.39 ± 0.03	0.34 ± 0.02
AMP (μmol/g)	0.07 ± 0.01	0.06 ± 0.02	0.09 ± 0.02	0.10 ± 0.03	0.09 ± 0.03	0.08 ± 0.02
Σ Ad (μmol/g)	2.46 ± 0.14	2.42 ± 0.14	2.28 ± 0.12	2.28 ± 0.09	2.67 ± 0.08	2.47 ± 0.14
EC	90 ± 1	90 ± 1	89 ± 1	89 ± 2	90 ± 1	90 ± 1
Lactate, brain tissue (μmol/g)	1.44 ± 0.27	2.58 ± 0.36*	3.46 ± 1.05*	3.57 ± 0.95	2.40 ± 0.85	2.07 ± 0.50
Pyruvate, brain tissue (μmol/g)	0.21 ± 0.01	0.26 ± 0.01*	0.26 ± 0.02	0.25 ± 0.02	0.22 ± 0.03	0.16 ± 0.01*
L/P ratio, brain tissue	9 ± 1	10 ± 1	14 ± 5	14 ± 5	12 ± 4	13 ± 3
Glucose, brain tissue (μmol/g)	2.28 ± 0.17	2.06 ± 0.17*	1.77 ± 0.22	1.67 ± 0.25	1.83 ± 0.35	2.01 ± 0.28

See text for abbreviations.

* Significant difference from values at normal CPP and Pa_{CO_2} = 40 mmHg, $P < 0.05$.

Comparison of the present ISF results with previous studies of NTG, SNP, and TMP from this laboratory demonstrates that the disturbances of cerebral metabolism and EEG seen here with the combination of hypocapnia and ISF-induced hypotension were less than those previously reported during hypocapnia plus hypotension induced with those other hypotensive treatments. With hypocapnia plus NTG- or SNP-induced hypotension, the power of the α and β_2 spectra of the EEG decreased at CPP ≤ 60 mmHg, and at CPP of 40 mmHg CBF, the EC, and brain tissue PCr fell while the L/P ratio in brain tissue increased.[6,7] With hypocapnia plus TMP-induced hypotension, α and β_2 activity decreased at CPP ≤ 60 mmHg, β_1 activity, brain tissue PCr, and the EC decreased at CPP ≤ 50 mmHg, and CBF and brain tissue glucose fell and the L/P ratio in brain tissue increased at CPP of 40 mmHg.[6] In contrast, hypocapnia plus ISF-induced hypotension was associated with no alteration of cerebral metabolites and no reduction of total EEG power.

Also, EEG recovery at 30 min after hypocapnia plus ISF-induced hypotension was more complete than EEG recovery from NTG, SNP, or TMP. After recovery from hypocapnia plus NTG- or SNP-induced hypotension, the power of the α and β_2 spectra of the EEG remained decreased, while after recovery from hypocapnia plus TMP-induced hypotension, the power of the α, β_1, and β_2 spectra of the EEG remained decreased.[6,7] In contrast, after recovery from hypocapnia plus ISF-induced hypotension,

TABLE 4. Systemic Variables during Measurement of CBF, CMR_{O_2}, and EEG (mean ± SEM) (n = 6)

	Normal CPP Pa_{CO_2} = 40 mmHg	Normal CPP Pa_{CO_2} = 20 mmHg	CPP = 60 mmHg Pa_{CO_2} = 20 mmHg	CPP = 50 mmHg Pa_{CO_2} = 20 mmHg	CPP = 40 mmHg Pa_{CO_2} = 20 mmHg	Normal CPP Pa_{CO_2} = 40 mmHg
Pa_{O_2} (mmHg)	152 ± 13	162 ± 13*	146 ± 13	137 ± 12	144 ± 14	145 ± 11
Pa_{CO_2} (mmHg)	40.6 ± 1.1	22.1 ± 0.7*	21.7 ± 0.3*	22.3 ± 0.7*	22.8 ± 0.5*	41.5 ± 1.0
*p*H	7.34 ± 0.01	7.50 ± 0.02*	7.47 ± 0.02*	7.46 ± 0.02*	7.45 ± 0.02*	7.29 ± 0.01
Bicarbonate (mEq/l)	21.5 ± 0.7	17.4 ± 0.8*	15.4 ± 0.7*	15.8 ± 0.7*†	15.9 ± 0.5*†	19.6 ± 0.8
Hb (g/dl)	13.6 ± 0.6	13.6 ± 0.7	13.6 ± 0.6	13.4 ± 0.6	13.3 ± 0.6	13.3 ± 0.5
CPP (mmHg)	118 ± 6	116 ± 6	59 ± 1*†	50 ± 1*†	40 ± 1*†	109 ± 7
Heart rate (beats/min)	116 ± 6	123 ± 8	128 ± 5	129 ± 5	127 ± 4	115 ± 9
Temperature, nasopharyngeal (° C)	37.2 ± 0.1	37.2 ± 0.1	36.9 ± 0.1	37.0 ± 0.2	36.9 ± 0.1	36.9 ± 0.1
Lactate, arterial (μmol/ml)	2.83 ± 0.24	3.66 ± 0.36*	4.22 ± 0.48*	4.04 ± 0.50*	3.97 ± 0.46*	3.27 ± 0.42
Pyruvate, arterial (μmol/ml)	0.22 ± 0.01	0.28 ± 0.02	0.27 ± 0.01	0.24 ± 0.01†	0.20 ± 0.01	0.15 ± 0.01*
L/P ratio, arterial	13 ± 1	13 ± 1	16 ± 1	17 ± 2	20 ± 2	21 ± 2*
Glucose, arterial (mg/dl)	124 ± 5	130 ± 9	103 ± 6†	103 ± 5*†	100 ± 7*†	106 ± 15
ISF concentration, end-expired (%)	0.33 ± 0.02	0.34 ± 0.02	2.04 ± 0.24*†	2.39 ± 0.21*†	2.67 ± 0.21*†	0.33 ± 0.02

See text for abbreviations.

* Significant difference from values at normal CPP and Pa_{CO_2} = 40 mmHg, $P < 0.05$.

† Significant difference from values at normal CPP and Pa_{CO_2} = 20 mmHg, $P < 0.05$.

TABLE 5. Systemic Variables during Measurement of Brain Tissue Metabolites (mean ± SEM) (n = 6)

	Normal CPP Pa_{CO_2} = 40 mmHg	Normal CPP Pa_{CO_2} = 20 mmHg	CPP = 60 mmHg Pa_{CO_2} = 20 mmHg	CPP = 50 mmHg Pa_{CO_2} = 20 mmHg	CPP = 40 mmHg Pa_{CO_2} = 20 mmHg	Normal CPP Pa_{CO_2} = 40 mmHg
Pa_{O_2} (mmHg)	148 ± 10	156 ± 12	162 ± 12	148 ± 15	150 ± 17	154 ± 5
Pa_{CO_2} (mmHg)	40.2 ± 1.3	20.7 ± 0.6*	19.1 ± 0.5*	19.9 ± 0.3*	20.3 ± 1.0*	38.8 ± 0.6
*p*H	7.34 ± 0.02	7.51 ± 0.02*	7.51 ± 0.02*	7.47 ± 0.02*	7.44 ± 0.03*	7.29 ± 0.02
Bicarbonate (mEq/l)	21.2 ± 0.5	17.3 ± 0.0*	15.6 ± 0.05*†	15.9 ± 0.5*	16.1 ± 0.5*	19.8 ± 0.3
Hb (g/dl)	13.4 ± 0.5	13.4 ± 0.5	13.3 ± 0.5*	13.1 ± 0.5	12.9 ± 0.4	13.1 ± 0.6
CPP (mmHg)	119 ± 8	122 ± 4	59 ± 1*†	50 ± 1*†	40 ± 1*†	114 ± 8
Heart rate (beats/min)	109 ± 4	113 ± 4	113 ± 5	113 ± 4	113 ± 3	102 ± 5
Temperature, nasopharyngeal (° C)	37.2 ± 0.2	37.2 ± 0.2	37.2 ± 0.2	37.1 ± 0.52*	37.0 ± 0.2	36.9 ± 0.2
Lactate, arterial (μmol/ml)	2.31 ± 0.31	3.32 ± 0.41*	3.43 ± 0.37*	3.41 ± 0.52	3.19 ± 0.46*	2.84 ± 0.38
Pyruvate, arterial (μmol/ml)	0.15 ± 0.03	0.18 ± 0.03*	0.18 ± 0.03	0.15 ± 0.02*†	0.13 ± 0.04†	0.12 ± 0.06
L/P ratio, arterial	16 ± 2	17 ± 3	19 ± 4	21 ± 4	25 ± 8	24 ± 4*
Glucose, arterial (mg/dl)	135 ± 9	131 ± 4	127 ± 8	114 ± 8*	109 ± 7*	117 ± 9
ISF concentration, end-expired (%)	0.32 ± 0.02	0.33 ± 0.02	1.92 ± 0.18*†	2.28 ± 0.20*†	2.59 ± 0.26*†	0.33 ± 0.02

See text for abbreviations.

* Significant difference from values at normal CPP and Pa_{CO_2} = 40 mmHg, $P < 0.05$.

† Significant difference from values at normal CPP and Pa_{CO_2} = 20 mmHg, $P < 0.05$.

the power of all EEG spectra were similar to those during the initial period of normal CPP and Pa_{CO_2}.

The combination of hypocapnia plus ISF-induced hypotension caused disturbances that were greater than those observed with hypocapnia plus SNP-induced hypotension, but similar to those observed with NTG- or TMP-induced hypotension.[6,7] Arterial blood lactate and/or the L/P ratio was increased during hypocapnia plus hypotension and at 30 min after recovery from hypocapnia plus hypotension in both of the ISF groups in this study. By comparison, no elevation of arterial blood lactate or the L/P ratio was observed during hypocapnia combined with SNP-induced hypotension. With regard to the integrity of the experimental preparation, the following indicators of intact cerebral vasculature and metabolic pathways were observed here: 1) cerebral vasoconstriction with hypocapnia; 2) metabolic changes consistent with stimulation of brain tissue phosphofructokinase by hypocapnia (glucose consumption and lactate and pyruvate production); 3) autoregulation of CBF at CPP of ≥ 50 mmHg; and 4) restoration of cerebral energy stores and metabolites with reperfusion posthypotension.[6,7] In addition, the results of this study are consistent with those of previous studies with respect to the following: 1) the per cent reduction of CMR_{O_2} relative to the per cent increase of ISF[1,36]; lower CBF (and a higher ratio of CBF reduction to CMR_{O_2} reduction) during ISF-induced hypotension at hypocapnia than at normocapnia[1,4]; preservation of EEG activity at ISF concentrations of less than 3.0% end-expired[37]; and a time-related decrease of CBF with cannulation of the sagittal sinus or torcular.[38,39] Dogs were not examined at normocapnia and ISF-induced hypotension as controls for hypocapnia and ISF-induced hypotension because previous studies reported no change in cerebral energy stores or metabolites where CPP was lowered to 22 mmHg with ISF[1] and minimal changes when MAP was lowered to 30–32 mmHg with ISF plus hemorrhage.[40]

In summary, this study found that the reduction of CBF caused by combining hypocapnia with ISF-induced hypotension did not lead to deterioration of cerebral energy stores or metabolites or the EEG. In contrast to previous studies of hypocapnia combined with hypotension induced by SNP, TMP, or NTG, only ISF prevented deterioration of cerebral metabolism and EEG during hypocapnia combined with hypotension. Moreover, only ISF prevented EEG abnormalities following restoration of normocapnia and normotension. For hyperventilated patients, ISF may be preferred as a hypotensive treatment over SNP, TMP, or NTG.

TABLE 6. Brain Biopsy Values at the Conclusion of Studies to Measure CBF, CMR_{O_2}, and EEG (mean ± SEM) (n = 6)

	Normal CPP Pa_{CO_2} = 40 mmHg
PCr (μmol/g)	5.96 ± 0.94
ATP (μmol/g)	2.11 ± 0.10
ADP (μmol/g)	0.36 ± 0.03
AMP (μmol/g)	0.10 ± 0.03
Σ Ad (μmol/g)	2.57 ± 0.08
EC	89 ± 1
Lactate, brain tissue (μmol/g)	1.77 ± 0.41
Pyruvate, brain tissue (μmol/g)	0.19 ± 0.02
L/P ratio, brain tissue	9 ± 3
Glucose, brain tissue (μmol/g)	1.87 ± 0.21

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