

## The Effect of Acute Hypocapnia on Local Cerebral Blood Flow during Middle Cerebral Artery Occlusion in Isoflurane Anesthetized Rats

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**Background:** Because the effect of hypocapnia on distribution of cerebral blood flow during focal cerebral ischemia is controversial, this investigation was performed in rats to determine whether hypocapnia, instituted immediately after the onset of focal cerebral ischemia, produces a favorable redistribution of blood flow (an "inverse steal") toward the ischemic territory.

**Methods:** After surgical preparation during normocapnic isoflurane anesthesia, middle cerebral artery occlusion (MCAO) was performed. Animals were randomized to either immediate institution of hypocapnia ( $n = 9$ ;  $P_{aCO_2}$   $23 \pm 2$  mmHg) or continued normocapnia ( $n = 8$ ;  $P_{aCO_2}$   $40 \pm 2$  mmHg). Thirty minutes thereafter, local cerebral blood flow (l-CBF) was determined autoradiographically using  $^{14}C$ -iodoantipyrine. Local cerebral blood flow was determined in four coronal brain sections spanning the distribution of the middle cerebral artery. For the hemisphere ipsilateral to MCAO, the areas of cortex in which CBF fell within three specified CBF ranges (0-6, 6-15, and 15-23 ml/100 g/min) were measured and expressed as a percentage of the total area of cortex in that section. In the hemisphere contralateral to MCAO, to confirm the presence of normal  $CO_2$  reactivity in non-ischemic brain in this model, average l-CBF was determined for the cortex, the subcortex, and the entire hemisphere in each coronal section.

**Results:** Hypocapnia resulted in significantly lower l-CBF in the cortex, subcortex, and entire hemisphere in all coronal sections of brain contralateral to MCAO. In the hemisphere

ipsilateral to MCAO, a favorable redistribution of CBF was not observed. For the three more anterior coronal sections (1-3), a significantly larger percentage of the cortex had l-CBF in the range of 15-23 ml  $\cdot$  100 g $^{-1}$   $\cdot$  min $^{-1}$  in the hypocapnia group animals. In sections 2 and 3, significantly larger areas of cortex had l-CBF in the range of 6-15 ml  $\cdot$  100 g $^{-1}$   $\cdot$  min $^{-1}$  in the hypocapnia group than in the normocapnia group. For all sections, there were no significant differences between hypocapnic and normocapnic groups in the area of cortex with l-CBF in the range of 0-6 ml  $\cdot$  100 g $^{-1}$   $\cdot$  min $^{-1}$ .

**Conclusions:** The current study does not provide evidence for the occurrence of a hypocapnia-induced inverse steal phenomenon during acute focal cerebral ischemia of 30 min duration in the rat. The data suggest that, rather than reducing the area of the critically ischemic brain, hypocapnia may increase the size of the region at risk. The data do not support the use of hypocapnia as a therapeutic measure to produce a favorable redistribution of CBF during focal cerebral ischemia of acute onset. (Key words: Anesthetics, volatile: isoflurane. Brain, ischemia: incomplete. Measurement techniques, cerebral blood flow: autoradiography. Ventilation: hypocapnia.)

SEVERAL investigations have suggested that hypocapnia may produce a favorable redistribution of cerebral blood flow (CBF), a so-called "inverse steal," during focal cerebral ischemia and might thereby serve to improve neurologic outcome.<sup>1-5</sup> These observations would argue that it should be advantageous to deliberately reduce arterial carbon dioxide tension in circumstances in which a focal ischemic episode has occurred (e.g., acute stroke) or might occur (e.g., cerebral vascular surgical procedures, interventional neuroradiology). By contrast, other investigations of hypocapnia during focal cerebral ischemia suggest that the inverse steal phenomenon occurs rarely, if at all, and that hypocapnia may not have any beneficial cerebral effects.<sup>4-10</sup> These latter observations have led to the common recommendation that normocapnia be maintained in circumstances in which focal cerebral ischemia might occur.

There have been numerous methodologic differences among the studies cited above, including the timing

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of the onset of hypocapnia, the duration of hypocapnia, and the duration of the ischemic episode. More troublesome is that, in some instances, the resolution of the CBF technique employed may have been insufficient to identify the redistribution of CBF in areas where distribution was most likely to have occurred and to have been of benefit. As a result, it is difficult to draw an unequivocal conclusion from the existing information as to whether hypocapnia does or does not produce a beneficial redistribution of CBF during focal cerebral ischemia. The current study, which employed autoradiographic determination of local cerebral blood flow (l-CBF), was undertaken to examine the acute effects of hypocapnia initiated rapidly after the onset of focal cerebral ischemia.

### Methods

The protocol was reviewed and approved by the Animal Use Subcommittee of the authors' institution. Seventeen male Sprague Dawley rats (Harlan, Indianapolis, IN) weighing 270–400 g were fasted overnight and allowed unrestricted access to water. On the day of the study, the animals were assigned alternately to either the hypocapnic group ( $n = 9$ ) or the normocapnic group ( $n = 8$ ). The animals were anesthetized in a plexiglass chamber with 4% inspired isoflurane in oxygen. Following induction of anesthesia, the trachea was intubated and the lungs were mechanically hyper-ventilated (tidal volume, 12 ml/kg; respiratory rate, 50 breaths/min). Carbon dioxide was added to the inspired gas mixture to maintain normocapnia ( $P_{aCO_2}$  35–40 mmHg) during the surgical preparation. Anesthesia was maintained with 1.9% inspired isoflurane (1.2 MAC<sup>11</sup>) in 40% oxygen, balance nitrogen. Vaporizer output was confirmed with a mass spectrometer (Ohmeda 6000, Multi-gasmonitor, Ohmeda, Atlanta, GA). The animals were paralyzed with a single dose of 0.2 mg pancuronium to facilitate the surgical preparation. Rectal temperature was maintained at 37° C by a servocontrolled heating pad. Both femoral arteries and veins were cannulated with PE50. One femoral artery was used for monitoring of mean arterial blood pressure (MAP), heart rate, arterial blood gases, and hematocrit. The other femoral artery was used for sampling of blood during isotope infusion. One femoral vein was used for infusion of maintenance intravenous fluids (4 ml/kg/h of normal saline). If necessary, phenylephrine was administered by infusion to maintain MAP between 100 and 120 mmHg during the study period. Any animal with an MAP greater than 120

mmHg or less than 100 mmHg was excluded from the study. The second femoral venous catheter was used for infusion of isotope at the time of blood flow determination. Small increments of sodium bicarbonate (0.25 mEq) were given intravenously as necessary to maintain arterial pH greater than 7.30.

Following insertion of the vascular catheters, the animal's head was secured in a head holder and a left subtemporal craniectomy was performed.<sup>12</sup> The dura was reflected and the left middle cerebral artery was exposed. The middle cerebral artery was occluded using microbipolar electrocautery under constant saline irrigation. The artery was occluded from a point proximal to the olfactory tract to a point just proximal to the intersection with the inferior cerebral vein. Care was taken to avoid injury to the latter structure.

Immediately following middle cerebral artery occlusion (MCAO), the inspired CO<sub>2</sub> concentration was either reduced to establish hypocapnia (20–25 mmHg) or continued to maintain normocapnia (35–40 mmHg) during the occlusion period.

### CBF Determination

Thirty minutes after MCAO, l-CBF was determined autoradiographically using <sup>14</sup>C-iodoantipyrine (<sup>14</sup>C-IAP). A dose of 75 μCi/kg of <sup>14</sup>C-IAP was dissolved in 1 ml of normal saline and was infused intravenously at an increasing rate over 46 s by an infusion pump. Concurrently, arterial blood was sampled on pre-weighed squares of Whatman 3-mm chromatography paper (Maidstone, England). As the isotope infusion concluded, the animals were decapitated and the brains were removed rapidly and frozen in 2-methyl butane cooled by liquid Freon.

The blood samples were sealed immediately in pre-weighed vials containing a scintillation cocktail composed of 5 ml of Aquamix scintillation solution (ICN Biomedicals, Costa Mesa, CA) and 200 μl of distilled water. The vial was agitated for 10 s. The blood was allowed to elute for 24 h prior to scintillation counting to determine <sup>14</sup>C concentration.

The frozen brains were cut at –15° C into 20-μ coronal sections at intervals of 100 microns. The sections were heat mounted on glass slides. The brain sections were placed on Kodak OM-1 film (Rochester, NY) along with <sup>14</sup>C standards (Amersham, Arlington Heights, IL) for 21 days.

The methods used for the determination of l-CBF are similar to those described previously.<sup>13</sup> A Drexel/Dumas image processing system (Drexel University Image

Processing Center, Philadelphia, PA) was used. The program employed was derived from the formulas originally described by Sakurada *et al.*<sup>14</sup>

In each animal, four coronal planes spanning the distribution of middle cerebral artery were analyzed. The sections were at 2.4-mm intervals with the first section 2.5 mm behind the frontal pole. In each coronal plane, measurements of I-CBF were made in two adjacent coronal sections and were averaged. The CBF determinations were made by an observer who was blinded to the experimental groups.

For the hemisphere ipsilateral to MCAO, the areas of cortex in which CBF was within three specified CBF ranges (0–6, 6–15, and 15–23 ml/100 g/min) were measured and expressed as a percentage of the total area of cortex in that section. On a *post hoc* basis, the three ranges were combined to permit a comparison of the areas falling in the CBF range 0–23 ml/100 g/min. In the hemisphere contralateral to MCAO, to confirm the presence of normal CO<sub>2</sub> reactivity in non-ischemic brain in this model, average I-CBF was determined for the cortex, the subcortex, and the entire hemisphere in each coronal section.

Between-group comparisons of physiologic and CBF data were performed using Student's *t* test for unpaired data. All results are expressed as mean  $\pm$  SD. A *P* value less than .05 was considered statistically significant.

## Results

The physiologic data are presented in table 1. At the time of the I-CBF determination, Pa<sub>CO<sub>2</sub></sub> was significantly

lower and pH was significantly higher in the hypocapnic group (22.5  $\pm$  1.6 mmHg and 7.48  $\pm$  0.03, respectively) than in the normocapnic group (39.8  $\pm$  1.5 mmHg and 7.31  $\pm$  0.03, respectively). There were no significant differences between groups for weight, MAP, heart rate, Pa<sub>O<sub>2</sub></sub>, and hematocrit, and for total dose and duration of administration of phenylephrine.

In the normocapnic group, coronal section number 4 was damaged during mounting in one animal. Accordingly, the data for that section represent the results of seven rather than eight animals.

Hypocapnia resulted in significantly lower I-CBF in the cortex, subcortex, and entire hemisphere in all coronal sections of brain contralateral to MCAO (table 2).

The areas of cortex ipsilateral to MCAO in which I-CBF fell within the ranges of 0–6, 6–15, 15–23, and 0–23 ml/100 g/min, expressed as a percentage of the total ipsilateral cortical area, are presented in table 3. For coronal sections 1, 2, and 3, a significantly larger percentage of the cortex had I-CBF in the ranges of 15–23 ml/100 g/min in the hypocapnia group animals. In sections 2 and 3, significantly larger areas of cortex had I-CBF in the range of 6–15 ml/100 g/min in the hypocapnia group than in the control group. For all sections, there were no significant differences between hypocapnic and normocapnic groups in the area of cortex with I-CBF in the range of 0–6 ml/100 g/min. For sections 1, 2, and 3, significantly (*P* < .035) larger areas of cortex had I-CBF in the range of 0–23 ml/100 g/min in the hypocapnia group than in the control group.

**Table 1. Physiologic Data Before MCAO and During MCAO**

	Before MCAO		During MCAO	
	Normocapnia	Hypocapnia	Normocapnia	Hypocapnia
MAP (mmHg)	105 $\pm$ 11	108 $\pm$ 7	111 $\pm$ 4	109 $\pm$ 5
Heart rate (beats/min)	363 $\pm$ 29	371 $\pm$ 28	341 $\pm$ 24	362 $\pm$ 36
Pa <sub>CO<sub>2</sub></sub> (mmHg)	41.1 $\pm$ 2.1	39.2 $\pm$ 2.0	39.8 $\pm$ 1.5	22.5 $\pm$ 1.6*
Pa <sub>O<sub>2</sub></sub> (mmHg)	177 $\pm$ 37	190 $\pm$ 41	177 $\pm$ 30	182 $\pm$ 48
pH	7.33 $\pm$ 0.02	7.34 $\pm$ 0.05	7.31 $\pm$ 0.03	7.48 $\pm$ 0.03*
Hematocrit (%)	41 $\pm$ 3	41 $\pm$ 3	36 $\pm$ 5	37 $\pm$ 3
Phenylephrine (average rate of infusion) ( $\mu$ g $\cdot$ kg <sup>-1</sup> $\cdot$ min <sup>-1</sup> )	—	—	6.4 $\pm$ 3.0	7.0 $\pm$ 2.2
Duration of phenylephrine	—	—	45 $\pm$ 47	55 $\pm$ 36
Weight (g)	345 $\pm$ 22	343 $\pm$ 39	—	—

Values are mean  $\pm$  SD. MCAO =middle cerebral artery occlusion.

\* *P* < .05 hypocapnia versus normocapnia for MCAO data.

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Table 2. The l-CBF for the Hemisphere, Cortex, and Subcortex of the Brain Contralateral to MCAO for Coronal Sections 1-4

	Section 1			Section 2		
	Hemisphere	Cortex	Subcortex	Hemisphere	Cortex	Subcortex
Normocapnia	224 ± 58	214 ± 53	233 ± 67	233 ± 64	224 ± 68	240 ± 61
Hypocapnia	112 ± 43*	103 ± 39*	122 ± 52*	115 ± 41*	103 ± 37*	126 ± 47*
	Section 3			Section 4		
	Hemisphere	Cortex	Subcortex	Hemisphere	Cortex	Subcortex
Normocapnia	207 ± 39	206 ± 42	208 ± 40	218 ± 34	176 ± 16	257 ± 52
Hypocapnia	113 ± 45*	101 ± 42*	121 ± 49*	130 ± 64*	94 ± 43*	165 ± 103*

Values are given as mean ± SD ( $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ ). l-CBF = local cerebral blood flow; MCAO = middle cerebral artery occlusion.

\*  $P < .05$  hypocapnia versus normocapnia.

## Discussion

The intent of the current study was to determine whether hypocapnia can produce a favorable redistribution of CBF toward ischemic areas of the brain in the setting of acute focal cerebral ischemia. The CBF ranges examined were chosen on the basis of human and animal investigations that have delineated CBF thresholds corresponding to critical events during cerebral ischemia. Astrup *et al.*, using a model of MCAO in baboons, demonstrated that a CBF of 6 ml/100 g/min or less was associated with the massive intracellular potassium release indicative of imminent cellular demise.<sup>15</sup> The CBF range 0-6 ml/100 g/min was chosen to represent brain regions in which neurons are at risk of imminent demise. Branston *et al.*, also using a model of MCAO in baboons, demonstrated a loss of evoked responses at a CBF of approximately 15 ml/100 g/min.<sup>16</sup> The flow range between these two thresholds, 6-15 ml/100 g/

min, was chosen to represent regions in which neurons are electrically quiescent, but viable for a period determined by the severity of the CBF reduction within that range. This range is often referred to as the ischemic penumbra.<sup>15</sup> Investigations in animal subjects suggest that the earliest signs of neural dysfunction can occur with CBF in the range of 20-23 ml/100 g/min.<sup>17-19</sup> The flow range of 15-23 ml/100 g/min was chosen to represent brain near the thresholds for developing significant ischemia. These particular thresholds (6, 15, and 23 ml/100 g/min) were selected in part because they represent the work of one laboratory in one species.<sup>15-17</sup> No comparable body of data exists for the rat. However, investigations of cerebral ischemia in gerbils by Crockard *et al.* indicate that, despite differences in resting CBF in normal brain, these physiologic thresholds, in particular the threshold for massive potassium release, are similar in another rodent

Table 3. Area of Cortex Ipsilateral to MCAO in Which CBF Fell within Four l-CBF Ranges: 0-6, 6-15, 15-23, 0-23  $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  in Coronal Brain Sections 1-4

	Section 1				Section 2			
	0-6	6-15	15-23	0-23	0-6	6-15	15-23	0-23
Normocapnia	7.5 ± 4.6	4.3 ± 2.1	4.6 ± 1.9	16.4 ± 6.8	8.1 ± 2.8	4.5 ± 1.4	4.2 ± 2.0	16.8 ± 3.3
Hypocapnia	14.2 ± 9.1	8.8 ± 6.3	8.3 ± 4.0*	31.3 ± 14.2*	13.4 ± 11.9	8.2 ± 3.3	7.7 ± 3.5*	29.3 ± 13.4*
	Section 3				Section 4			
	0-6	6-15	15-23	0-23	0-6	6-15	15-23	0-23
Normocapnia	0.2 ± 0.3	1.4 ± 1.9	2.4 ± 1.8	4.0 ± 3.8	0	0.14 ± 0.27	1.3 ± 2.0	1.5 ± 2.2
Hypocapnia	4.9 ± 10.6	5.4 ± 4.7*	6.5 ± 4.5*	16.9 ± 15.2*	2.5 ± 6.0	3.7 ± 6.3	4.0 ± 3.3	10.2 ± 13.8

Values are mean ± SD (expressed as a percent of the total area of the cortex).

MCAO = middle cerebral artery occlusion; l-CBF = local cerebral blood flow.

\*  $P < .05$  hypocapnia versus normocapnia.

species.<sup>20,21</sup> Relevant investigations have been performed in rats. However, in most instances interpretation of the threshold information they provide is difficult either because the duration and/or degree of ischemia prior to the threshold event is unclear or because, when the endpoint was histologic, the CBF was measured at only one point during a prolonged ischemic episode. One of those investigations indicates a minimum threshold for potassium release of 15 ml/100 g/min in cortex,<sup>22</sup> and two others place the CBF threshold for histologic damage at 19 and 25 ml/100 g/min.<sup>23,24</sup> Because of the uncertainties as to the precise thresholds in rats, the data analysis also included a grouping of the three ranges into a single range, 0–23 ml/100 g/min. This range, if the investigations just cited<sup>23,24</sup> are more accurate representations of critical thresholds, may be considered to be the territory at risk for histologic damage in the event of persistent ischemia.

The present investigation was designed on the basis of the rationale that a favorable, hypocapnia-induced redistribution of CBF should reduce the area of brain falling within these CBF ranges, in particular within the two lower flow ranges. A favorable redistribution of CBF was not observed. In fact, hypocapnia during MCAO resulted in increases in the area of cortex within the CBF ranges of 6–15 ml/100 g/min and 15–23 ml/100 g/min.

The theory of redistribution of CBF by vasoconstrictor influences from areas of well perfused brain to areas of low CBF was put forward by Brawley<sup>25</sup> and Lassen and Palvolgyi<sup>2</sup> and has been referred as the inverse or Robin Hood<sup>2</sup> steal phenomenon. There have been numerous subsequent investigations involving measurements of CBF that have attempted to confirm the occurrence of a hypocapnia-induced inverse steal in the setting of focal cerebral ischemia. The results of these investigations have been inconsistent. Brawley observed, in the ischemic hemisphere of hypocapnic dogs, an increase in CBF in only 2 of 10 animals studied during MCAO. In the other eight animals there was a decrease in CBF.<sup>1</sup> Lassen and Palvolgyi attested to the occurrence of inverse steals in humans, but their abstract provided no details.<sup>2</sup> Pistolesse *et al.* measured CBF in a small series of patients undergoing carotid endarterectomy. Only one of seven patients demonstrated any evidence of a favorable redistribution of CBF as measured by a xenon clearance technique.<sup>4</sup> Yamaguchi *et al.* saw no evidence of inverse steal in cats made acutely hypocapnic beginning 4–6 h after

MCAO.<sup>5</sup> In fact, they observed that I-CBF was significantly lower in the ischemic hemisphere of hypocapnic animals as compared with those in which normocapnia was maintained.

There also have been investigations in the setting of traumatic brain injury. Cold *et al.* measured CBF (intra-carotid <sup>133</sup>Xe washout technique) in 26 comatose adults and observed “rare” instances of apparent inverse steal.<sup>26</sup> However, these events were limited to areas where initial CBF was “low” and were more likely to occur in patients whose eventual outcome was poor. Darby *et al.* have made an anecdotal report of a comparable phenomenon in a patient with a severe closed head injury.<sup>27</sup> In that patient, hyperventilation was associated with an increase in CBF in a region where the baseline flow was “severely decreased,” and the patient survived in a vegetative state.

A number of additional investigations have examined the effect of hypocapnia in the setting of focal cerebral ischemia using endpoints other than CBF. The majority of these investigations have identified either no benefit<sup>6–8</sup> or a deleterious effect.<sup>9,10</sup> Only an investigation by Soloway *et al.* suggested a beneficial effect.<sup>28</sup> Those authors observed improved neurologic outcome when hypocapnia was initiated prior to MCAO and maintained for 2 h. It appears from the report that the MCA remained occluded until the animals were sacrificed 7 days after surgery. The reasons for the dramatic beneficial effects of a short interval of hypocapnia despite continued cerebral ischemia are unclear, although their report contains the information that “mean temperatures in the hyperventilated group were slightly lower than those in the control group.” We are not aware of any attempt to duplicate their results.

While the various investigations described above, considered collectively, do not present strong support for a beneficial effect of hypocapnia, there were several reasons for the present reexamination of the question. First, the majority of these investigations involved circumstances that differ from typical intraoperative events in which the periods of ischemia are short, and immediate implementation of hypocapnia can occur. Furthermore, a recent anecdotal report by Artru and Merriman<sup>3</sup> of an apparently favorable response to acute hypocapnia in the setting of electroencephalographic signs of ischemia induced by carotid cross-clamping appeared to warrant an examination of the CBF effects of hypocapnia induced rapidly after vessel occlusion. Second, a shortcoming of essentially all the previous investigations that have employed CBF as the endpoint

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is that they have examined relatively large brain regions (frequently the ischemic hemisphere). The experimental approach has been to choose a brain region (on the basis of the anticipated distribution of CBF reduction) and to measure the CBF therein. By contrast, the ideal methodology for investigations of this nature is one that chooses a CBF or range of CBF values (as determined by a knowledge of important physiologic thresholds) and measures the extent of brain regions in which they occur. More specifically, the limitation of previous approaches has been that a hypocapnia-induced decrease in average CBF could be largely the result of decreases in areas in which normal physiologic responses including CO<sub>2</sub> responsiveness persisted and in which residual CBF, while reduced, was compatible with survival. Cerebral blood flow may have increased in the most severely ischemic regions, but that increase could have been "lost" in the averaging of flow over a larger brain region. This shortcoming is avoided by the methodology used in the present study. This investigation nonetheless failed to confirm the occurrence of a favorable redistribution of CBF.

In the current study there was no evidence of an inverse steal despite the attractiveness of the theory as originally proposed by Lassen. We are uncertain as to the explanation for the nonoccurrence of the phenomenon. However, the increase in the percentage of cortex within the 1-CBF ranges of 6–15 and 15–23 ml/100 g/min in the hypocapnic animals is consistent with the possibility that brain regions immediately adjacent to the ischemic area have preserved CO<sub>2</sub> responsiveness and act as a barrier to redistribution of CBF from more remote regions of normally perfused brain. It is also possible that the failure to demonstrate an inverse steal occurred because the CBF measurements were made in the presence of an open craniotomy, in which circumstance the potentially favorable effect of hypocapnia on intracranial pressure and cerebral perfusion pressure could not occur.

In conclusion, the present study does not provide evidence for the occurrence of a hypocapnia-induced inverse steal phenomenon during acute focal cerebral ischemia of 30 min duration in the rat. In fact, hypocapnia resulted in significantly larger areas of cerebral cortex in which CBF fell in the ranges of 6–15 and 15–23 ml/100 g/min as compared to normocapnic animals. This suggests that, rather than reducing the area of the critically ischemic brain, hypocapnia may increase the size of the region at risk in the event of sustained ischemia. The data do not support the use of

hypocapnia as a therapeutic measure to produce a favorable redistribution of CBF during focal cerebral ischemia of acute onset.

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