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Hyperventilation-induced cerebral ischemia in patients with acute brain lesions: demonstration by xenon-enhanced CT.

W A Stringer, A N Hasso, J R Thompson, D B Hinshaw and K G Jordan

Hyperventilation-Induced Cerebral Ischemia in Patients with Acute Brain Lesions: Demonstration by Xenon-enhanced CT

Warren A. Stringer,[1,3,5] Anton N. Hasso,[1] Joseph R. Thompson,[1] David B. Hinshaw,[1] and Kenneth G. Jordan[2,4]

PURPOSE: To examine the possibility that hyperventilation, commonly used to prevent or treat increased intracranial pressure in patients with acute brain lesions, may induce significant cerebral ischemia. **METHODS:** Local cerebral blood flow and vascular reactivity were measured before and after hyperventilation using xenon-enhanced CT in 12 patients with acute brain lesions. **RESULTS:** Five patients showed "paradoxical" reactivity (increased cerebral blood flow during hyperventilation) within the lesions. In five patients, hyperventilation induced ischemia in apparently normal regions of brain. In three patients, areas of luxury perfusion became ischemic during hyperventilation, while in three patients, lesions with moderate ischemia became more ischemic. Most patients showed more than one type of reactivity. **CONCLUSIONS:** These findings document hyperventilation-induced ischemia in acute brain lesions, and demonstrate that this phenomenon affects both injured and apparently intact areas of the brain. Further studies are required to determine the clinical significance of these pathophysiologic changes.

Index terms: Brain, ischemia; Cerebral blood, flow; Computed tomography, xenon study; Xenon, cerebral blood flow

Acute elevation of intracranial pressure (ICP) is associated with severe underlying brain injury from many causes (1). Hyperventilation is an effective and commonly used method to acutely reduce ICP (2). Its mechanism is thought to involve hypocapnia leading to cerebrospinal fluid alkalosis and cerebral vasoconstriction, with reduction of cerebral blood flow (CBF) and cerebral blood volume. Reduction of ICP occurs rapidly

and may be maintained for hours to days if hyperventilation is continued.

Cerebral vasoreactivity may be lost or diminished as a result of many pathologic processes, including head trauma (3, 4), stroke (5, 6), and chronic ischemia (7–9). This is thought to be due to dilation of vessels within the lesions from the initial insult. In theory, these areas may have increased perfusion during hyperventilation, as blood is shunted into them from adjacent areas with greater vasoreactivity. This phenomenon has been termed an "inverse steal" (10). In such cases, any reduction of ICP achieved by hyperventilation is likely due to vasoconstriction in uninjured, vasoreactive areas of the brain (2).

Because of the complexity of these relationships, and out of concern for the possibility of hyperventilation-induced ischemia, we began to examine CBF directly by xenon computed tomography (CT) in patients who were being hyperventilated for reduction or prevention of increased ICP. Our preliminary results raise concern about the safety of hyperventilation in this setting.

Methods

Twelve patients were referred for CBF measurement. These included four patients with closed head trauma, two with asphyxia, three with stroke, and three with meningitis. One patient with a left hemisphere stroke was studied twice, 7 days apart, and was anesthetized for each procedure. The remaining patients were comatose and were pharmacologically paralyzed to prevent involuntary motion. The initial patients were studied at the request of their attending physician, to help determine appropriate ventilatory management. Later patients were studied under a protocol approved by the Institutional Review Board.

End tidal carbon dioxide ($ETCO_2$) was continuously monitored during the procedure in all patients, and mean arterial pressure in all but two. ICP was monitored in five patients, allowing calculation of the cerebral perfusion pressure (mean arterial pressure minus ICP). All patients were monitored by a physician and a critical care nurse during the procedure. The patients were ventilated by respiratory therapists who adjusted the rate and volume of ventilation to achieve a constant $ETCO_2$. Because of variation in the type and severity of brain injury between individual patients, uniform $ETCO_2$ values could not be employed. Instead, limits were determined for each patient in consultation with their attending physician. The examination parameters for each patient are summarized in Table 1.

Xenon CT was performed on a GE 9800 Quick system in 11 patients, using hardware and software supplied by the manufacturer. The details of this procedure have been described previously (11, 12). For one patient, xenon CT was performed on a Siemens DR-H scanner, for which the procedure is similar. Three levels of the brain were studied in each patient. Following the initial xenon CT, 20 minutes were allowed to elapse for xenon washout. The rate of ventilation was changed and the new $ETCO_2$ stabilized during this time. Xenon CT was then repeated without

additional delay. The entire dual xenon CT procedure was accomplished in approximately 1 hour.

Analysis of Results

Region of interest measurements were made at corresponding locations on the high and low $ETCO_2$ scans for each patient. Apparently intact regions of brain, injured regions with luxury perfusion, and injured regions with ischemia were all examined. A region was considered to be intact if it showed no abnormality on baseline conventional CT, and had blood flow above ischemic threshold (see below). In many cases, these regions were known to be uninvolved by the pathologic process responsible for disease elsewhere in the brain. All regions with flow below ischemic threshold at the higher level of $ETCO_2$ were classified as injured with ischemia, regardless of their appearance on the baseline scans. Injury with luxury prefusion was identified by blood flow above ischemic threshold in a patient with a severe global insult, or in a region that was clearly abnormal by conventional CT in a patient with focal injury. Dysfunction within regions of luxury perfusion was confirmed by electroencephalogram and/or clinical examination. Confirmation of the assignment of each region of the brain into one of these three categories was also obtained by follow-up CT or magnetic resonance whenever possible.

Normal gray matter blood flow is 60–80 mL/100 g/min for awake young adults; values of 32–55 mL/100 g/min may be normal in coma (13) (D. Marion and H. Yonas, personal communication). Cortical dysfunction becomes clinically evident when flow falls below an ischemic threshold of approximately 23 mL/100 g/min (14). Infarction may occur at flow less than 16–18 mL/100 g/min, (14) depending on both the duration and severity of ischemia. While these threshold values were obtained initially in experimental animals (15), similar thresholds have been found using xenon CT in humans (16, 17) (Stringer WA,

TABLE 1: Physiologic parameters during first and second xenon-CT studies

Patient No.	Age (years)/Sex	Disease Process	ET-CO$_2$	MAP	ICP	CPP
1	40/F	ICA dissection	24 → 18	90 → 101	15 → 6	75 → 95
2	20/F	MCA embolus	40 → 30	85 → 80		
			30 → 40	80 → 70		
3	67/M	Head trauma	41 → 31			
4	3/M	Asphysia	19 → 24	99 → 101	6 → 25	93 → 86
5	6 mo/M	Meningitis	26 → 37	115 → 98		
6	11 mo/F	Meningitis	37 → 26	80 → 75		
7	5/M	Hypoxia	32 → 42	85 → 70		
8	6/M	Head trauma	25 → 19	99 → 100	14 → 18	85 → 82
9	8/M	Head trauma Cardiac arrest	26 → 18.5	92 → 87	25 → 23	67 → 64
10	6/M	Meningitis	37 → 25			
11	1 mo/F	Head trauma	20 → 8	81 → 80	41 → 31	40 → 49
12	57/M	Thrombosis in MCA aneurysm	27 → 36			

Note.—ETCO$_2$ = end tidal CO$_2$, mm Hg; MAP = main arterial pressure, mm Hg; ICP = intracranial pressure, mm Hg; CPP = cerebral perfusion pressure (= MAP − ICP), mm Hg; MCA = middle cerebral artery; ICA = internal carotid artery.

unpublished data). Normal white matter flow is approximately 20 mL/100 g/min (12), but ischemic and infarct thresholds are less clear for white matter. White matter flow may also be less accurately measured by xenon CT than flow in gray matter (18). For these reasons, the white matter findings in our patients, while generally similar to the gray matter results, were excluded from analysis.

In seven patients, CBF was measured initially at the higher of two ETCO$_2$ values and subsequently at the lower. In five patients, CBF was measured at the lower value first, due to hyperventilation during transport to the CT suite. However, to maintain mathematical consistency, CO$_2$ reactivity was calculated in all patients as if the ETCO$_2$ change was from higher to lower. CO$_2$ reactivity was expressed as percent change in CBF per one Torr change in ETCO$_2$ concentration, and was calculated as:

$$\text{reactivity} = 100 * \frac{(CBF_2 - CBF_1)/CBF_1}{CO_{2-2} - CO_{2-1}}$$

where CBF$_1$ and CO$_{2-1}$ are the values at the higher ETCO$_2$ and CBF$_2$ and CO$_{2-2}$ are at the lower ETCO$_2$.

The degree of CO$_2$ reactivity was then classified as hyperreactive (greater than 5% change in CBF/Torr), normoreactive (1%-5% change in CBF/Torr), hyporeactive (less than 1% change in CBF/Torr), and paradoxical (increasing CBF with decreasing ETCO$_2$), based on normal CO$_2$ reactivity values of approximately 3% change in CBF/Torr (12, 13). CO$_2$ reactivity was also examined according to whether CBF was reduced from above to below ischemic threshold, or vice versa.

The inherent error of xenon CT, incorporating a 95% confidence interval, is approximately 15% (12) (D. Gur, personal communication). Regions of interest which showed paradoxical CO$_2$ response were therefore excluded unless the change in CBF was at least 21% of the flow measured at the higher ETCO$_2$ (15% × 1.414, to account for repeated measurement). Also, all areas which showed a nonparadoxical CBF change of less than 21% were considered to be hyporeactive, even if the change was greater than 1%/mm Hg ETCO$_2$ (see Fig. 2B). Since there is potential for increased measurement error at very low flow levels, regions of interest that showed flow less than 10 mL/100 g/min at both high and low ETCO$_2$ were not analyzed further. These exclusions will decrease sensitivity by increasing the likelihood that a true effect of ETCO$_2$ change will be discounted, but will increase specificity.

Results

Four patients had a global brain injury. At the higher of the ETCO$_2$ values, the other eight patients had regions of apparently intact brain, with CBF above ischemic threshold. Seven patients showed regions of injury with luxury perfusion, and nine patients showed regions of injury with ischemia. Nearly all patients showed several types of vasoreactivity, which are summarized in Table 2. Several types of reactivity judged to be of

particular clinical relevance are summarized in Table 3 and are discussed below. No patient demonstrated a significant change in the degree of cerebral edema, mass effect, or herniation, as determined by evaluation of the baseline CT images before and after hyperventilation. None of the patients whose ICP was monitored showed a significant change in this parameter during the xenon inhalation. No patient showed a change in neurologic status as a result of the study procedure.

1. Eight patients had regions of apparently intact brain with baseline flow above ischemic threshold. In five of these, local CBF fell below ischemic threshold in at least one such region as ETCO$_2$ was reduced. These results indicate the possibility of uninjured tissue being inadvertently placed at risk of ischemia or infarction. In the subgroup of five patients whose ICP was monitored, this pattern was seen in one patient (Fig. 1), in whom it occurred against an increase in cerebral perfusion pressure (CPP). Therefore, it

TABLE 2: CO$_2$ reactivity by patient

Patient No.	Uninjured Brain	Injured-Luxury Perfusion	Injured-Ischemic
1	I[1], N[1], P	I[1], N	I[1], P[2]
2	I[1], N[1], D	I, D	P[2]
3	I[1], N, D	———	P
4	———	I[1], N, D	P, D
5	I, N, D	———	———
6	I[1], N[1], D	———	I, N
7	———	D, P	P[2]
8	D, P	D	D
9	———	N, D	———
10	N, D	———	———
11	———	I[1], N[1]	N
12	N[1], D	———	P

Note.—Superscripts indicate the presence of at least one region of interest showing: [1] = CBF falling from above to below ischemic threshold; [2] = paradoxical rise in CBF from below to above ischemic threshold. I = hyperreactivity; N = normal reactivity; D = hyporeactivity; P = paradoxical reactivity.

TABLE 3: Percentage of patients with hyperventilation-induced ischemia or paradoxical reactivity

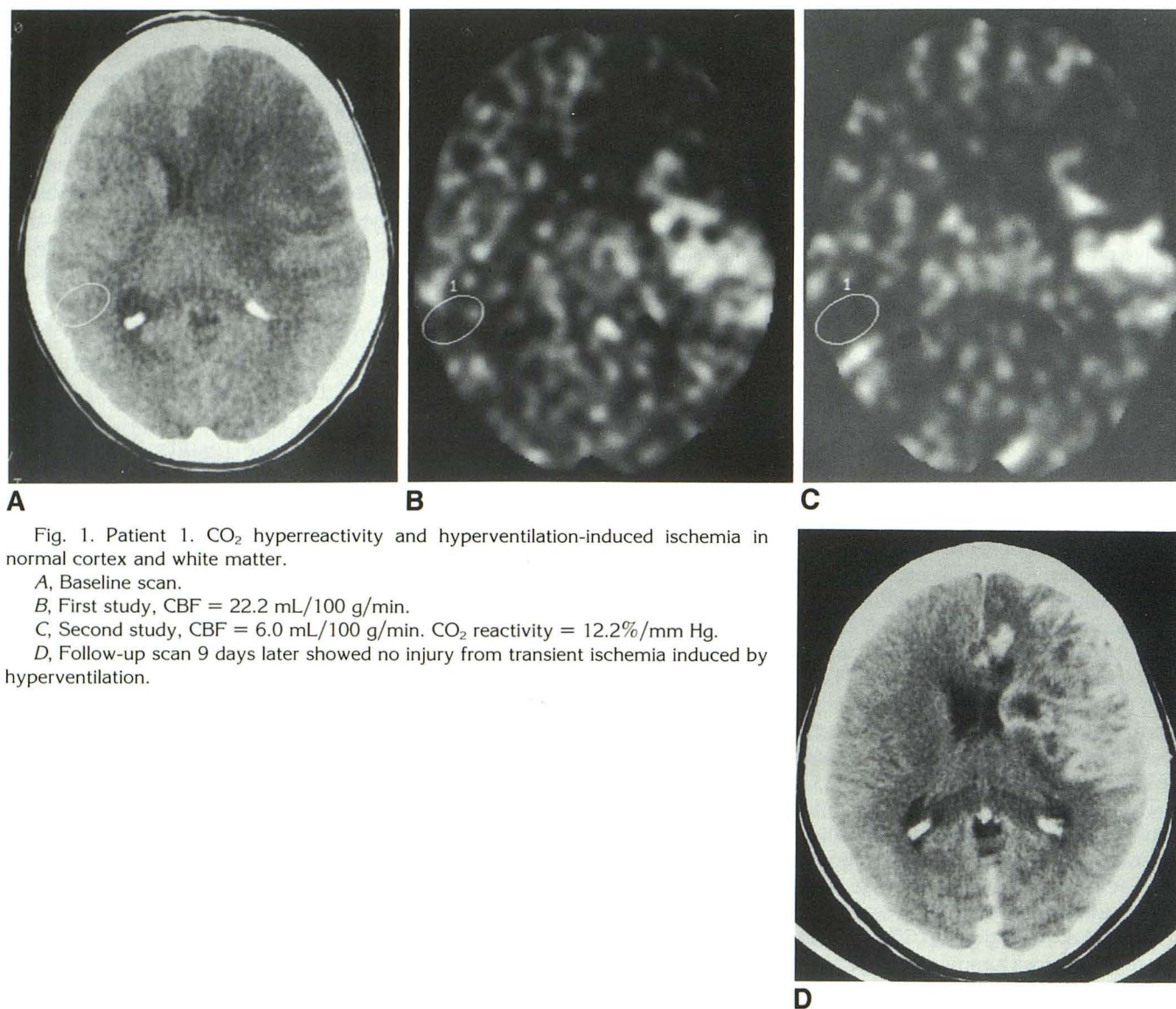| Tissue Character and Response	All Patients	ICP-Monitored Patients
Uninjured brain (hyperventilation-induced ischemia)	62.5	20
Luxury-perfused injured brain (hyperventilation-induced ischemia)	57.2	60
Ischemic injured brain (additional decrease in CBF)	33.3	40
Ischemic injured brain (paradoxical CBF rise to above ischemic level)	33.3	20

A   B   C

Fig. 1. Patient 1. CO_2 hyperreactivity and hyperventilation-induced ischemia in normal cortex and white matter.

A, Baseline scan.

B, First study, CBF = 22.2 mL/100 g/min.

C, Second study, CBF = 6.0 mL/100 g/min. CO_2 reactivity = 12.2%/mm Hg.

D, Follow-up scan 9 days later showed no injury from transient ischemia induced by hyperventilation.

D

could have resulted neither from hemodynamic changes alone nor from a loss of pressure autoregulation.

2. Seven patients had injured regions with luxury perfusion (Fig. 2). In three of these (not illustrated), all with ICP monitored, flow fell below ischemic threshold in these regions as $ETCO_2$ was reduced. In each case, the fall in CBF occurred against an increase in CPP. These results indicate the presence of preserved or hyperreactive CO_2 response in regions of luxury perfusion, and raise the possibility of ischemic reinjury to already injured tissue.

3. Nine patients had regions of injury with ischemia. As $ETCO_2$ was reduced a further decline in CBF was seen in three (Fig. 3). Two of these patients had ICP monitored, and in each

the reduction in CBF occurred against an increase in CPP. These cases show preservation or accentuation of CO_2 response in ischemic injured tissue, and again raise the possibility of additional injury resulting from hyperventilation.

4. "Paradoxical reactivity" (increasing CBF of 21% or greater despite reduction in $ETCO_2$) involving ischemic regions was seen in several patients. Of the nine patients with ischemia in injured tissue, a rise in CBF which remained below ischemic threshold was seen in four, and a rise in CBF from below to above ischemic threshold was present in three (Fig. 4). Of note, in four patients, both preserved reactivity in apparently intact or luxury perfused regions and paradoxical reactivity in ischemic regions were seen concurrently.
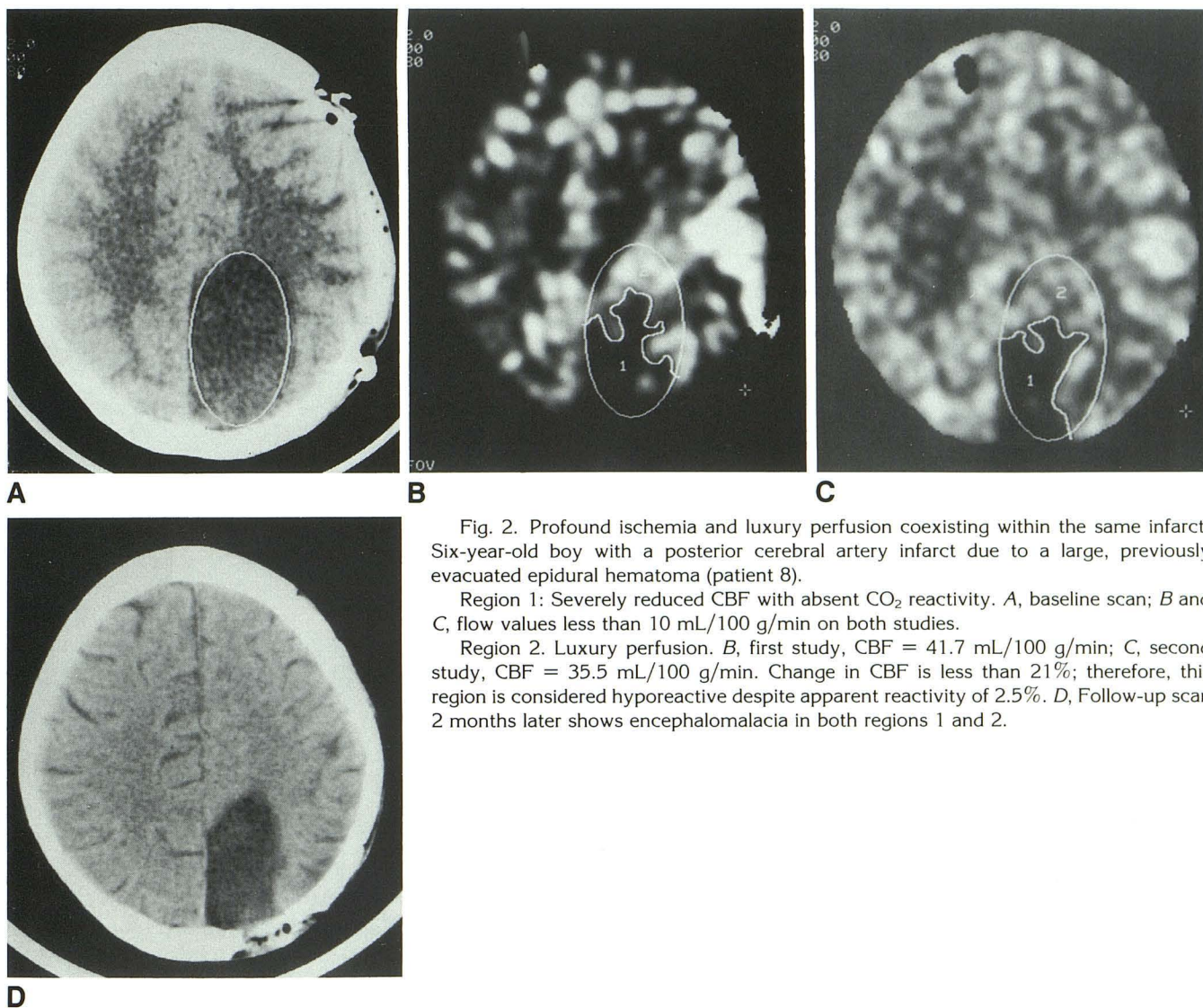
A   **B**   **C**

Fig. 2. Profound ischemia and luxury perfusion coexisting within the same infarct. Six-year-old boy with a posterior cerebral artery infarct due to a large, previously evacuated epidural hematoma (patient 8).

Region 1: Severely reduced CBF with absent CO_2 reactivity. A, baseline scan; B and C, flow values less than 10 mL/100 g/min on both studies.

Region 2. Luxury perfusion. B, first study, CBF = 41.7 mL/100 g/min; C, second study, CBF = 35.5 mL/100 g/min. Change in CBF is less than 21%; therefore, this region is considered hyporeactive despite apparent reactivity of 2.5%. D, Follow-up scan 2 months later shows encephalomalacia in both regions 1 and 2.

D

Of the five patients with ICP monitoring, two showed regions of paradoxical CO_2 reactivity, which caused CBF to rise from below to above the ischemic threshold in one. In both cases, this occurred together with an increase in the cerebral perfusion pressure. In these two patients, the increased CBF during hyperventilation may be explained by concurrent failure both of normal CO_2 reactivity and of pressure autoregulation, with pressure-passive flow responding to the increased CPP (Fig. 5). Significantly, in both patients, other regions showed preserved CO_2 reactivity, with hyperventilation-induced reduction of CBF below ischemic levels. In two other patients, CPP did not change significantly, and no paradoxical CBF response was observed. In the fifth patient, CPP declined in parallel with $ETCO_2$, but a paradoxical increase in CBF was still ob-

served in several apparently intact and luxury-perfused injured regions. This may be related to local "inverse steal" effects.

Discussion

Xenon Effects on CBF and ICP

In recent years, the question of flow activation (ie, increased CBF during xenon inhalation), and its effect on the quantitative accuracy of xenon CT measurement of CBF, has been raised. In normal volunteers, transcranial Doppler has shown an increase in middle cerebral artery blood velocity, indicative of increased distal tissue perfusion, of up to 40% beginning approximately 1.5 minutes into xenon inhalation (19, 20). However, three recent computer simulation studies have shown the resulting error in the CBF meas-
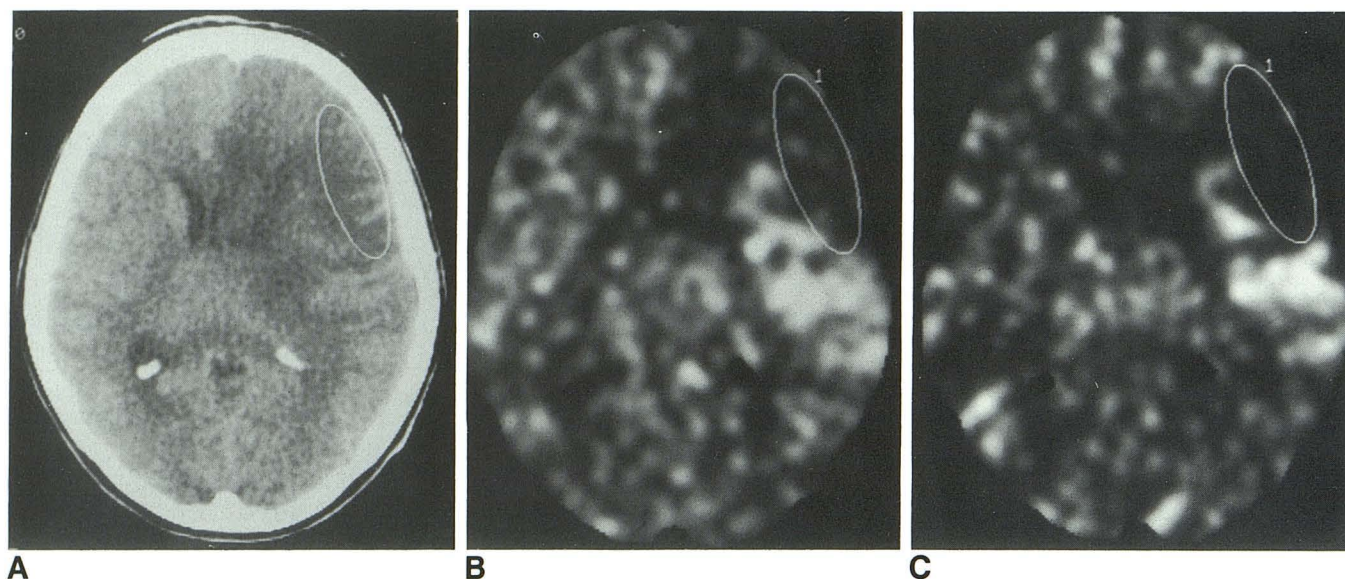
Fig. 3. Left middle cerebral artery infarct with ischemia and CO_2 hyperreactivity. Forty-year-old woman with acute left internal carotid artery dissection (patient 1).

A, baseline scan showing infarct in this area.

B, First study, CBF = 14.4 mL/100 g/min.

C, Second study, CBF = 5.1 mL/100 g/min. CO_2 reactivity = 10.7%/mm Hg. Follow-up contrast-enhanced scan confirmed extensive infarct (see Fig. 1D).

urement to be small, on the order of 5% or less for normal gray matter, and slightly higher for lower flow areas (21–23). Flow activation effects should have little influence on the results of the present study, since they should be similar for both the pre- and posthyperventilation xenon scans. Therefore, no attempt was made to control or correct for them.

Concern also has been raised in the past regarding possible elevation of ICP during xenon inhalation, in part because of these flow activation effects. However, recent studies of patients with severe head injuries and continuous ICP monitoring have shown ICP to remain stable (24–26). In the present study, none of the patients whose ICP was monitored shows a clinically significant change in this parameter.

Physiology of Increased ICP and Effects of Hyperventilation

Because clinical signs of increased ICP are often unreliable, ICP may be monitored directly in patients with severe brain injury or disease (1). Normal ICP is 10–15 Torr. Sustained ICP greater than 15–20 Torr, or prolonged pressure waves greater than 25 Torr, are considered abnormal. Elevated ICP may reduce CBF directly and lead to cerebral ischemia (1, 27), or cause brain her-

niation (1). In head trauma, sustained and uncontrollable ICP greater than 30 Torr is usually fatal (28), and its reduction correlates with improved prognosis.

Normal brain is generally thought to be protected from hyperventilation-induced injury (2). The mechanism may be as follows: as hyperventilation causes CBF to fall, mild local tissue ischemia leads to increased anaerobic metabolism and production of lactic acid. Local lactate accumulation attenuates the vasoconstrictor response to hyperventilation and leads to vasodilation. This is felt to prevent further ischemia and development of injury (2). High PO_2 usually accompanies hyperventilation, and also helps to prevent ischemic injury.

In injured brain, partial or complete loss of CO_2 reactivity often occurs, and has been thought to protect the injured area from further ischemic insult during hyperventilation. Therefore, hyperventilation has been considered safe for both injured and uninjured areas of brain (2).

Adverse Effects of Hyperventilation

In contrast to the above assumptions, several lines of evidence suggest that hyperventilation may indeed have harmful cerebral effects. In premature infants, inadvertent excessive hyper-
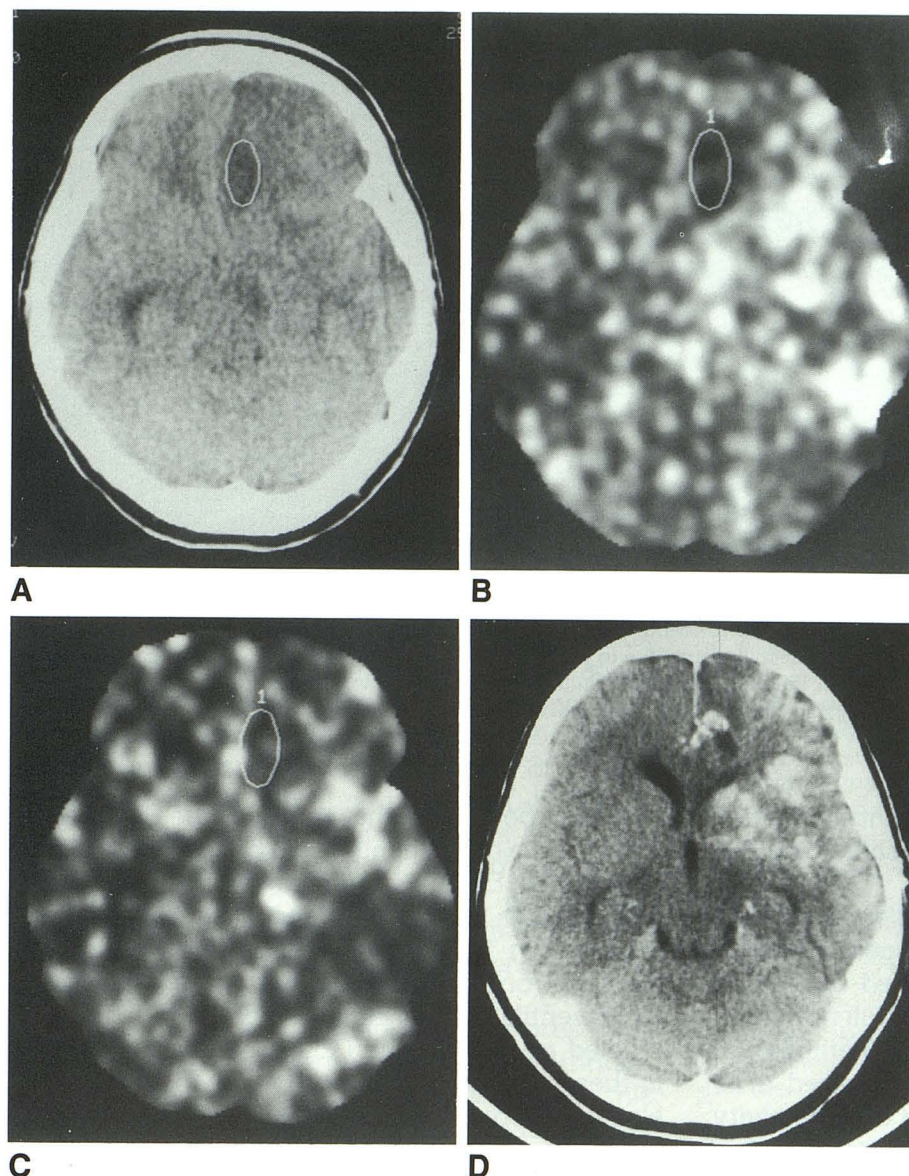
Fig. 4. Patient 1. Left anterior cerebral artery infarct with paradoxical CO_2 reactivity and absent autoregulation (pressure-passive CBF).

A, Baseline scan.

B, First study, CBF = 13.0 mL/100 g/min.

C, Second study, CBF = 24.9 mL/100 g/min. Paradoxical CO_2 response = −7.9%/mm Hg. Cerebral perfusion pressure rose from 79 to 95 mm Hg, and $ETCO_2$ fell from 24 to 18 mm Hg, between the first and second studies.

D, Follow-up scan with contrast confirms infarct in this area.

ventilation has been associated with a poor neurologic outcome, suggesting the possibility of permanent damage to the developing brain (29). In normal adults, hyperventilation induces changes in the electroencephalogram similar to those induced by hypoxia (30). These changes may be prevented if hyperbaric oxygen is administered simultaneously (Reivich M et al, paper presented at the American Academy of Neurology, Philadelphia, April 1966), but are more severe if there is concurrent hypoxia (31, 32). Hyperventilation can produce a doubling of cerebral anaerobic metabolism (33), an effect similar to that of hypoxia (34), and also decreases the oxygen tension of the cerebral cortex (35). In general, these effects have been found at PCO_2 levels below 20 Torr, and are less severe or not seen at higher levels of PCO_2.

A PCO_2 of 25 Torr has generally been considered safe for normal patients (2). Some authors have advised caution in patients with focal intracerebral disease (36, 37), as regional effects of hypocapnia can not be well evaluated by the methods that have been used in many of these studies. More recently, initial PCO_2 values of 25–35 Torr have been recommended for patients with elevated ICP, reserving more vigorous hyperventilation for ICP that remains uncontrolled (2). However, xenon CT studies of head injury patients (14, 38) have shown that PCO_2 levels in the 25–35 Torr range can be associated with either hyper- or hypoperfusion. The authors of
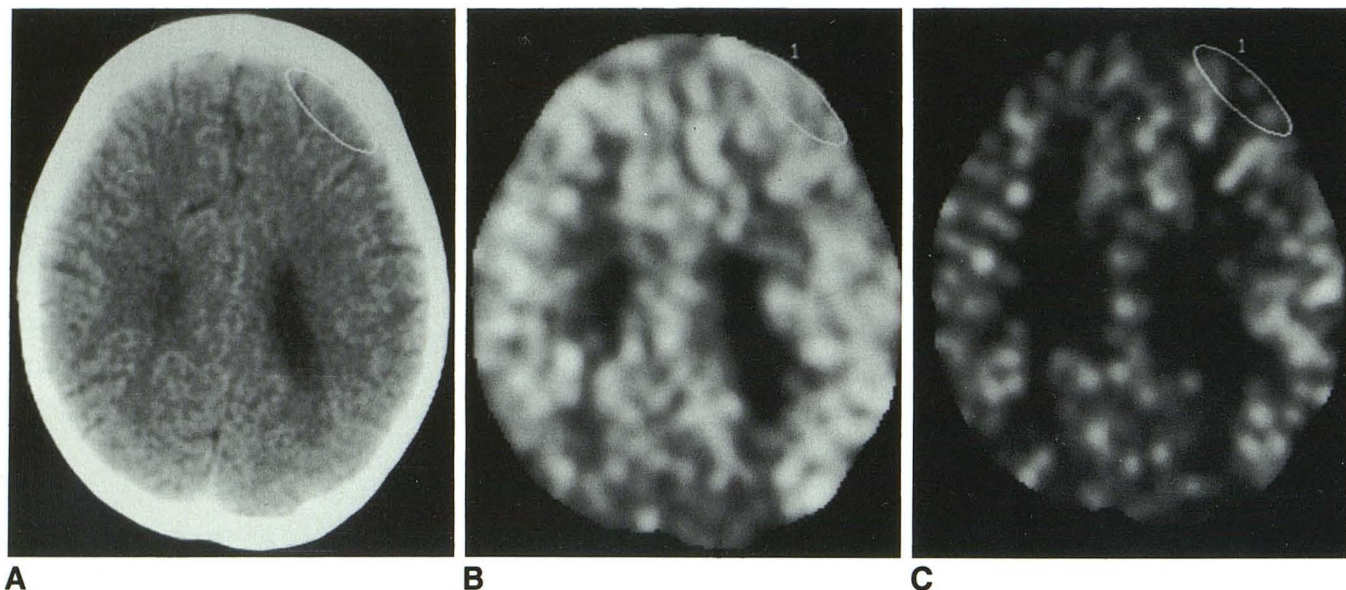
Fig. 5. Paradoxical CBF response to hyperventilation due to failure of normal CO_2 reactivity and autoregulation, with pressure-passive CBF. Five-year-old boy with diffuse hypoxic encephalopathy due to prolonged seizures (patient 7). $ETCO_2$ rose by 10 mm Hg and main arterial pressure fell by 15 mm Hg between the first and second studies. A, Baseline scan; B, first study, CBF = 49.8 mL/100 g/min; C, second study, CBF = 19.1 mL/100 g/min. Paradoxical CO_2 reactivity = −6.2%/mm Hg. Whole brain as well as regional CBF was affected in a similar fashion (B and C).

the latter studies have concluded that measuring flow values in each patient is advisable to guide hyperventilation therapy (13, 38).

There is also evidence to challenge the assumptions that the vasomotor response to CO_2 is abolished or diminished in injured regions of the brain, and that hyperventilation will not cause further injury to these areas. The vulnerability of the brain to ischemic insults is increased after trauma (39, 40). Partially preserved CO_2 reactivity has been found in stroke (41), and preserved or increased CO_2 reactivity in head trauma (13, 42). In subarachnoid hemorrhage, even with severe diffuse vasospasm, ICP above 40 Torr, and CBF reduced to 20 mL/100 g/min (below ischemic threshold), hyperventilation is still capable of reducing CBF further (43). A recent study of head trauma has shown worse outcome in patients treated with hyperventilation compared with patients who were not (44).

Shunting of blood into an injured area ("inverse steal") may result from regional differences in CO_2 reactivity. This may lead to increased edema and mass effect (38). It may also increase the likelihood of subsequent hemorrhage, as sometimes has been found with attempts to increase cerebral perfusion following ischemic events (45). In theory, such effects might also cause increased subfalcine or transtentorial herniation.

It may be argued that many of the changes in CBF seen in our patients could be transient effects of reduced $ETCO_2$, and that repeat scanning a few minutes later would show a return toward baseline. In this regard, the results in the five patients (one with ICP monitoring) who were hyperventilated during transport and initially studied at the lower $ETCO_2$ become important. In these patients a minimum of 30 to 45 minutes elapsed before the first flow measurement was obtained. One might expect transient CBF changes induced by hyperventilation to have resolved during this time. However, each type of vasoreactivity described above was seen in at least one of these patients, suggesting that the hyperventilation effects were, in fact, not transient. It should also be noted that these changes did not require severe hyperventilation, but were seen in two patients with $ETCO_2$ values above 30 mm Hg.

Our results confirm the complexity of the ventilation-CBF relationships in patients with diverse forms of brain injury. While the clinical significance of these findings remains unclear, we believe the possibility of induced ischemia should be considered whenever a patient is hyperventilated. The extreme hyperventilation that sometimes occur as a patient is transported is of particular concern. Our results also lend support

to a recent report which showed a worse outcome in head trauma patients who were treated with "routine" hyperventilation (44). Along with other authors (13, 38), we believe that routine hyperventilation should be avoided. Instead, it should be tailored to the individual patient and guided by serial evaluation of cerebrovascular physiology.

Measurement of ICP alone is insufficient to detect the regional effects seen in our patients. The same may be anticipated for bedside measurement of global cerebral perfusion and oxygen utilization. These relationships can only be evaluated by methods that examine local CBF and/or metabolism, including xenon CT, single photon emission computed tomography, positron emission tomography and possibly electroencephalogram. Unfortunately, with the exception of electroencephalogram and sometimes single photon emission computed tomography, these methods are difficult to use with severely ill or injured patients, and are not portable. We believe that electroencephalogram monitoring may be useful to identify potentially harmful effects of hyperventilation, which may then be more fully evaluated by one of the other methods described above. Although the clinical value of such an approach remains to be established, preliminary results at our institution have indicated its feasibility (Stringer WA et al, paper presented at the American Society of Neuroradiology, Orlando, FL, March 1989; and Jordan K, paper presented at the American Academy of Neurology, Cincinnati, OH, January 1988). We believe that this approach will allow a better understanding of the complex relationships between CBF, ICP, and cerebral function, and may lead to improved management of these severely ill patients.

Acknowledgments

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