Hypoxia, hyperoxia, ischemia, and brain necrosis

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Article abstract—*Background:* Human brains show widespread necrosis when death occurs after coma due to cardiac arrest, but not after hypoxic coma. It is unclear whether hypoxia alone can cause brain damage without ischemia. The relationship of blood oxygenation and vascular occlusion to brain necrosis is also incompletely defined. *Methods:* We used physiologically monitored Wistar rats to explore the relationship among arterial blood oxygen levels, ischemia, and brain necrosis. Hypoxia alone (PaO_2 = 25 mm Hg), even at a blood pressure (BP) of 30 mm Hg for 15 minutes, yielded no necrotic neurons. Ischemia alone (unilateral carotid ligation) caused necrosis in 4 of 12 rats, despite a $PaO_2 > 100$ mm Hg. To reveal interactive effects of hypoxia and ischemia, groups were studied with finely graded levels of hypoxia at a fixed BP, and with controlled variation in BP at fixed PaO_2. In separate series, focal ischemic stroke was mimicked with transient middle cerebral artery (MCA) occlusion, and the effect of low, normal, and high PaO_2 was studied. *Results:* Quantitated neuropathology worsened with every 10 mm Hg decrement in BP, but the effect of altering PaO_2 by 10 mm Hg was not as great, nor as consistent. Autoradiographic study of cerebral blood flow with ^{14}C-iodoantipyrine revealed no hypoxic vasodilatation during ischemia. In the MCA occlusion model, milder hypoxia than in the first series (PaO_2 = 46.5 ± 1.4 mm Hg) exacerbated necrosis to 24.3 ± 4.7% of the hemisphere from 16.6 ± 7.0% with normoxia (PaO_2 = 120.5 ± 4.1 mm Hg), whereas hyperoxia (PaO_2 = 213.9 ± 5.8 mm Hg) mitigated hemispheric damage to 7.50 ± 1.86%. Cortical damage was strikingly sensitive to arterial PaO_2, being 12.8 ± 3.1% of the hemisphere with hypoxia, 7.97 ± 4.63% with normoxia, and only 0.3 ± 0.2% of the hemisphere with hyperoxia ($p < 0.01$), and necrosis being eliminated completely in 8 of 10 animals. *Conclusions:* Hypoxia without ischemia does not cause brain necrosis but hypoxia exacerbates ischemic necrosis. Hyperoxia potently mitigates brain damage in this MCA occlusion model, especially in neocortex.
Key words: Hypoxia—Ischemia—Brain—Necrosis—Coma—Blood pressure—Cerebral blood flow.

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It is common but incorrect in clinical neuroscience to use the term "hypoxic/ischemic brain damage," relating or equating hypoxia and ischemia pathophysiologically.[1] Profound arterial hypoxia is usually seen in young patients with respiratory obstruction such as asthma, anaphylaxis, epiglottitis, croup, or bronchiolitis,[2-4] whereas brain ischemia is usually seen in older patients with atherosclerosis of the coronary or carotid arteries. Ischemia rarely complicates the hypoxia seen in young patients, and patients with stroke usually do not have accompanying systemic hypoxia.

Hypoxia is also distinct from ischemia pathophysiologically. In hypoxic hypoxia (i.e., hypoxia produced by lowering inspired oxygen content), cerebral blood flow (CBF) is actually increased,[5] whereas by definition, CBF is lowered during ischemia. Hypoxia impairs delivery of only oxygen. Glucose and other substances are still supplied by the blood, and metabolic products, such as lactate and H^+ ions, continue to be removed by the augmented blood flow. Most humans subjected to acute hypoxia have a normal EEG.[6] Hypoxia often does not cause neurologic deficits in humans exposed to severe ($PaO_2 < 30$ mm Hg; < 4 kPa) hypoxia[4,7] or extreme ($PaO_2 < 20$ mm Hg; < 2.7 kPa) hypoxia.[2,3] Autopsy examination after severe hypoxia has failed to show necrosis or other neuropathologic changes,[4] correlating with the lack of permanent neurologic deficit after coma due to pure hypoxia.

Experimentally as well as clinically, pure hypoxic insults fail to cause necrotizing brain damage. If systolic blood pressure was maintained over 65 mm Hg, no damage was seen from hypoxic hypoxia in cats.[8] As opposed to ischemia, hypoxia does not lead to release of excitatory amino acids.[9] Histotoxic hypoxia using sulfide or cyanide yields no brain necrosis unless profound and prolonged collapse of thesystemic circulation occurs.[10,11] Together, these controlled experimental results throw into question the entire concept of purely hypoxic brain damage in all its forms, be it hypoxic or histotoxic.

The role of the oxygen molecule in ischemic brain damage is also unclear. For over two decades,

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oxygen-derived free radicals have been proposed to play a role in cerebral ischemia, especially during the reperfusion phase.[12] Purely hyperoxic brain damage does exist at normal atmospheric pressures in the neonate,[13] but hyperbaric pressures are required to produce hyperoxic necrosis in the adult animal.[14] Artificially high arterial oxygen tension might theoretically exacerbate ischemic damage by augmented production of oxygen-derived free radicals in the border zone of focal ischemia, or at any brain location during reperfusion.[15]

We used two models to study the effects of varying arterial blood oxygenation separately from ischemia using focal ischemia of the middle cerebral artery (MCA), and studied high as well as normal and low arterial oxygen tensions in relation to quantitated brain necrosis.

Methods. A total of 184 male Wistar rats (Charles River Breeding Center, St. Constant, Quebec) weighing 250 to 350 grams were used—135 in the Levine (bilateral carotid occlusion plus hypertension) series, 19 in the autoradiographic measurement of CBF, and 30 in the MCA oxygenation experiments. Animals were housed in cages with sawdust-covered floors and kept on a 12:12-hour light-dark cycle at 24 °C. Rat chow and water were accessible ad libitum. All animals were treated in accordance with the guidelines of the Canadian Council on Animal Care.

Rats in all series were anesthetized with 4% halothane in 60% N_2O and 40% O_2, intubated (PE-240 tubing) under the guidance of a fiber optic light source (Intralux 4000; Volpi, Switzerland), and ventilated on a Starling type ventilator (Harvard Apparatus, Bournemouth, England) with 1% halothane in 60% N_2O and 40% O_2. The tail artery was cannulated (PE-50 tubing) and connected to a pressure transducer (Gould P50). Blood pressure (BP) readings were digitized, displayed, and recorded every 5 seconds by computer. Arterial pH, $PaCO_2$, and PaO_2 were intermittently sampled with a blood gas analyzer (model 1304, Instrumentation Laboratories, Milan, Italy). Blood glucose was also measured pre and post hypoxia and/or ischemia. A lateral tail vein was cannulated and connected to a compact syringe pump (Harvard model 975, South Natick, MA) infusing 0.9% normal saline at an infusion rate of 0.84 mL/hour. The bipolar interhemispheric EEG was monitored (figure 1) and intermittently recorded. Rectal temperature was monitored continuously and kept close to 37 °C with a thermistor-regulated servo-controlled heating blanket (Harvard, Edenbridge, Kent, England), and a 60-W heating lamp was maintained symmetrically positioned above the skull. After surgery, the halothane was discontinued and the rats were immobilized with suxamethonium chloride (Sigma, St. Louis, MO).

Levine series. The rats in these series (n = 135) were divided into hypoxia only, hypoxia with ischemia, and ischemia only groups.

To induce hypoxia only, after ~15 minutes, the inspired oxygen was lowered to give an arterial PaO_2 of 25 mm Hg. Tidal volume was adjusted when necessary throughout the experiment to maintain $PaCO_2$ in the normal range. To counteract systemic acidosis, a peripheral IV infusion of sodium bicarbonate (1 M, 0.84 mL/hour) was given during hypoxia to maintain blood pH > 6.9. Hypoxia led immediately to a marked reduction in BP. Because of the known sensitivity of ischemic damage to small differences in BP,[16] the mean arterial BP (MABP) was fixed at 30 mm Hg for 15 minutes (see figure 1) by adjusting the fractional inspiratory oxygen concentration (FiO_2). Hypoxia was stopped by reoxygenation with 100% O_2, and rats were extubated when spontaneous breathing was strong and constant. Arterial blood was sampled before, during, and after hypoxia.

To study hypoxia and ischemia simultaneously, ligation of the right common carotid artery was combined 1 day later with reduction in inspired oxygen content to achieve the desired PaO_2, and simultaneous exsanguination as needed to clamp MABP to the desired level without the use of pharmacologic agents. Two series (table 1) were done, one varying MABP at a constant PaO_2 and the second varying PaO_2 at a clamped MABP. In one series of five groups, hypoxia was induced to a PaO_2 of 25 mm Hg by lowering the FiO_2, and when this induced the MABP to spontaneously fall to 30, 40, 50, 60, or 70 mm Hg, the FiO_2 was adjusted to maintain the desired MABP for 15 minutes. In a separate series of four groups, hypoxia was induced to a PaO_2 of 25, 35, or 45 mm Hg, or > 100 mm Hg (normoxia), by adjusting the FiO_2. The PaO_2 = 25, MABP = 30 mm Hg group was a member of both series, as shown in table 1. MABP was kept at 30 mm Hg for 15 minutes by regulating the FiO_2 in the PaO_2 25, 35, and 45 mm Hg groups, or by rapid withdrawal or reinfusion of blood via the central venous catheter in the PaO_2 > 100 mm Hg group (8.4 ± 0.3 mL blood withdrawn). In the PaO_2 25, 35, and 45 mm Hg groups, blood withdrawal was also performed as in the PaO_2 > 100 mm Hg group (6.0 ± 0.5 mL blood withdrawn), if MABP did not fall to 30 mm Hg within 45 minutes during hypoxia. After this period of time, the shed blood was reinfused, and rats were reoxygenated with 100% oxygen. The rats were extubated and returned to their cages after recovery from anesthesia.

In all groups, the animals were allowed access to food and water in the postoperative period. After 1 week, they were anesthetized with 4% halothane in 40% O_2 and 60% N_2O, and perfused transcardially with 4% phosphate-buffered formaldehyde solution. The brains were removed on the following day and cut into 5-mm slices, processed in graded ethanols and xylol, and embedded in paraffin.

Each brain was serially sectioned (8 μm thick) at 500-μm intervals with a sliding microtome (model Hn 40, Reichert-Jung), from a rostral limit of bregma +2.2 mm to bregma −6.8 mm caudally. Animals that died spontaneously (see Results) before the 1-week survival period were excluded from analysis. The sections were stained with hematoxylin and eosin, and examined under a light microscope.

To quantitate brain damage, the infarcted area on sections of each of 18 coronal levels was traced using microcomputer-based digital image analysis (Jandel video analysis software JAVA, version 1.41, Jandel Scientific Inc., San Rafael, CA). Because significant atrophy was also present in the ischemic hemisphere, total tissue loss was calculated by summing the areas of cortical necrosis, striatal necrosis, and atrophy (difference between the hemispheres). Volumes of hemispheric tissue loss were determined by integrating the areas of damage in the anteroposterior dimension, from the rostral to the caudal section. Interindividual variation in brain size was controlled

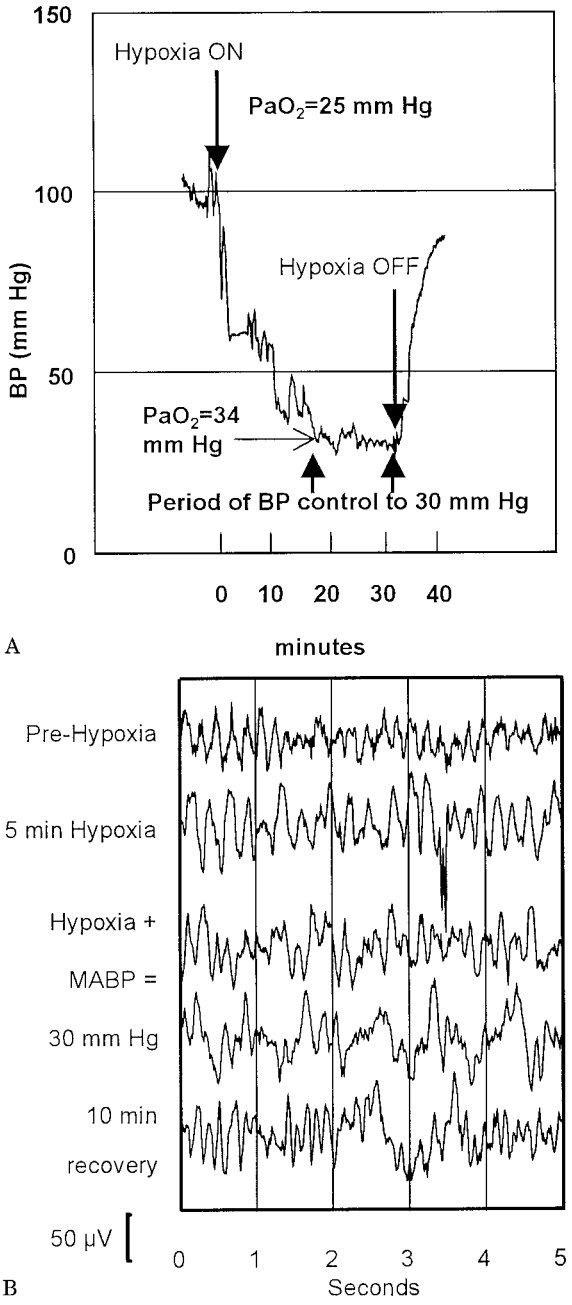

Figure 1. Recording of mean arterial blood pressure (MABP) and EEG before, during, and after the insult. (A) From an animal with hypoxia only, the typical immediate drop in MABP is seen. When MABP fell to 30 mm Hg, it was maintained at 30 mm Hg for 15 minutes by adjusting oxygen content and exsanguination/reinfusion of shed blood as necessary, delivering a 15-minute combined insult. Reoxygenation was done with 100% oxygen. (B) Representative 5-second strips of EEG sampled before hypoxia, and during hypoxia with hypotension to 30 mm Hg. Some slowing of EEG frequencies occurs, with high amplitude δ waves during hypoxia. Note that isoelectricity of the interhemispheric EEG is not seen.

for by dividing the volume of tissue loss by the contralateral hemispheric volume, expressing damage as a percent[16] rather than as raw data in mm^3. The hippocampus was sampled at six coronal levels encompassing the entire septotemporal axis, and the percentage of necrotic neurons in CA1 was calculated. All data were expressed as mean ± standard error (SEM). Physiologic variables (tables 1 and 2) were analyzed using one-way analysis of variance (ANOVA) followed by Scheffé test for individual group comparisons. The percentages of tissue volume loss and CA1 necrotic neurons were analyzed using the Kruskal-Wallis test followed by the Mann-Whitney *U* test, and by arcsine transformation followed by ANOVA.

Autoradiographic measurement of CBF. Nineteen male Wistar rats were divided into four groups: normal control (n = 4), hypoxia only (n = 5), ischemia only (n = 6), and hypoxia with ischemia (n = 4). Hypoxia, ischemia, and the combination of the two were produced by methods identical to those described above for the histologic series, except that the PaO_2 was regulated to 35 mm Hg in the hypoxia and hypoxia with ischemia groups. By the methods described above, MABP was controlled to ≈30 mm Hg, except in controls. Local CBF (lCBF) was measured using 4-iodo-^{14}C-antipyrine (^{14}C-IAP) as described by Sakurada et al.[17] Briefly, femoral venous and arterial lines were placed to allow injection and sampling, respectively, of radioisotope for CBF measurement. Fifty μCi of ^{14}C-IAP (50 mCi/mmol, Amersham Laboratories, Buckinghamshire, England) in 0.5 mL of 0.9% saline was infused via the femoral vein over a period of 30 seconds by a Harvard 944 infusion pump after at least 10 minutes of stable MABP at 30 mm Hg. Arterial blood samples were taken every 5 seconds to assess ^{14}C activity. Immediately after a circulation time of 30 seconds in the normoxia and ischemia groups, or 60 seconds in the hypoxia and hypoxia with ischemia groups (due to their slower circulation), the rats were decapitated. Brains were removed rapidly and frozen in isopentane cooled to −60 °C with dry ice, and stored in a freezer at −70 °C until prepared for autoradiography. At that time, brains were cut into 20-μm sections in a cryostat (Frigocut 2800, Leica Instruments, Germany) and were exposed to x-ray film (Hyperfilm βmax, Amersham) for 7 days, together with ^{14}C-methyl methacrylate standard (range 31 to 874 nCi/g). Plasma ^{14}C radioactivity was measured with a scintillation counter (Beckman LS 6800 series, liquid scintillation system, Beckman Instruments, Irvine, CA). The density of the autoradiograms was measured using an image analysis system (JAVA version 1.41, Jandel Scientific Inc.) via computer-based densitometry. LCBF was calculated by using a tissue-blood partition coefficient of 0.8 and the equation of Sakurada et al.[17]

Oxygenation in MCA ischemia. A total of 30 male Wistar rats were equally divided into normoxia (40% O_2 in ventilation gas), hypoxia (PaO_2 controlled to 45 mm Hg by varying the FiO_2), and hyperoxia (100% O_2 in inspired gas) groups. Core body temperature and ipsilateral temporalis muscle temperature were monitored and maintained at 37.5 °C using a thermistor-regulated servo-controlled heating blanket and overhead lamp during MCA occlusion.

MCA occlusion was done as previously reported.[16] The 3-0 nylon suture was advanced until a feeling of faint resistance was encountered. PaO_2 was adjusted to the desired levels in each group. MABP was also controlled to 60 mm Hg. This was done by rapid withdrawal or reinfusion of blood via the central venous catheter in the hyperoxia and normoxia groups (5.5 ± 0.4 and 5.1 ± 0.5 mL, respectively), and by adjusting the FiO_2 in the hypoxia group.

Table 1 *Groups—physiologic variables*

Variable	Hypoxia only	Hypoxia with ischemia							
		Groups varying MABP				Both series*	Groups varying PaO_2		
BP (mm Hg)	30	70	60	50	40	30	30	30	30
PaO_2 (mm Hg)	25	25	25	25	25	25	35	45	>100 mm Hg†
n	13	5	10	9	8	9	15	9	12
Preischemia									
MABP (mm Hg)	100.8 ± 3.1	116.4 ± 6.6	107.3 ± 3.4	105.2 ± 3.8	106.6 ± 3.2	98.6 ± 2.2	103.7 ± 2.5	102.1 ± 3.7	100.8 ± 2.8
PaO_2 (mm Hg)	148.5 ± 4.4	133.8 ± 9.0	149.2 ± 6.1	173.3 ± 6.3	158.7 ± 7.0	126.6 ± 9.9	151.5 ± 5.3	146.4 ± 9.6	121.0 ± 6.5
$PaCO_2$ (mm Hg)	33.8 ± 1.1	38.6 ± 2.2	37.9 ± 0.9	35.4 ± 1.0	36.5 ± 0.7	34.8 ± 1.4	35.5 ± 1.0	39.4 ± 0.9	36.4 ± 0.7
pH	7.39 ± 0.01	7.40 ± 0.03	7.42 ± 0.01	7.53 ± 0.02	7.43 ± 0.02	7.39 ± 0.02	7.42 ± 0.02	7.40 ± 0.01	7.37 ± 0.01
Hematocrit (%)	44.0 ± 1.2	44.0 ± 1.4	45.9 ± 1.2	45.8 ± 1.0	46.4 ± 0.9	48.2 ± 1.2	4.0 ± 0.8	45.0 ± 1.1	46.4 ± 0.5
Body temperature (°C)	37.5 ± 0.1	37.5 ± 0.1	37.5 ± 0.1	37.5 ± 0.1	37.5 ± 0.1	37.5 ± 0.1	37.4 ± 0.1	37.5 ± 0.1	37.5 ± 0.1
Glucose (mM)	9.6 ± 0.6	10.1 ± 0.8	11.3 ± 2.0	10.4 ± 1.1	11.6 ± 0.4	11.9 ± 1.4	11.1 ± 0.5	10.2 ± 0.3	11.4 ± 0.6

Values are mean ± SEM. *p* Values derived from one-way ANOVA followed by Scheffé test.

* This group is a member of both series (varying MABP and varying PaO_2).
† Inspired oxygen content was constant during experiment.

Suxamethonium chloride was injected IV to immobilize animals. After 80 minutes occlusion, the nylon suture was removed and the external carotid artery was tied permanently. MABP and PaO_2 were restored to preischemic levels by reinfusion of blood and adjusting the FiO_2, respectively. Halothane was discontinued and the animals were allowed to awaken.

One week after MCA occlusion, rats were perfused-fixed and the brain was removed, paraffinized, and serially sectioned (8 μm thick) at 500-μm intervals with a sliding microtome. The sections were stained with hematoxylin-eosin, and polygons for necrosis in the neocortex and in subcortical structures (white matter, deep gray) were traced separately, as were the areas of the ipsilateral and contralateral hemispheres. Brain tissue loss was then quantified as mm^3 by integrating necrosis and atrophy in the third, orthogonal axis. Volumes were finally normalized to the opposite hemisphere to control for variation in absolute brain size, being expressed as % of the hemisphere.

Results. *Physiologically monitored/controlled Levine preparation.* Severe hypoxia caused immediate cardiac hypotension (see figure 1), and preliminary experiments revealed that it was very difficult for rats to survive hyp-

Table 2 *Physiologic variables in the cerebral blood flow study*

Variable	Normal (n = 4)	Hypoxia only (n = 5)	Ischemia only (n = 6)	Hypoxia with ischemia (n = 4)
Prehypoxia/ischemia				
MABP (mm Hg)	112.2 ± 4.6	105.2 ± 5.2	94.1 ± 5.3	114.6 ± 3.6
PaO_2 (mm Hg)	152.8 ± 9.2	131.8 ± 8.5	139.7 ± 4.5	120.3 ± 18.3
$PaCO_2$ (mm Hg)	36.9 ± 2.0	39.7 ± 1.6	35.5 ± 1.8	36.7 ± 1.5
pH	7.39 ± 0.01	7.40 ± 0.02	7.41 ± 0.02	7.40 ± 0.02
Hematocrit (%)	43.8 ± 1.1	45.0 ± 1.0	44.2 ± 0.9	45.0 ± 2.3
Glucose (mM)	12.2 ± 1.9	10.6 ± 1.2	12.3 ± 1.2	12.9 ± 1.9
During control of MABP				
MABP (mm Hg)	—	33.0 ± 1.8*	34.1 ± 1.2*	33.9 ± 2.1*
PaO_2 (mm Hg)	—	35.4 ± 2.5*	—	33.0 ± 1.5*
$PaCO_2$ (mm Hg)	—	34.7 ± 3.3	—	34.2 ± 1.2
pH	—	7.29 ± 0.02	—	7.28 ± 0.04

Values are mean ± SEM. *p* Values derived from one-way ANOVA followed by Scheffé test.

* $p < 0.001$ Compared with normal group.

MABP = mean arterial blood pressure.

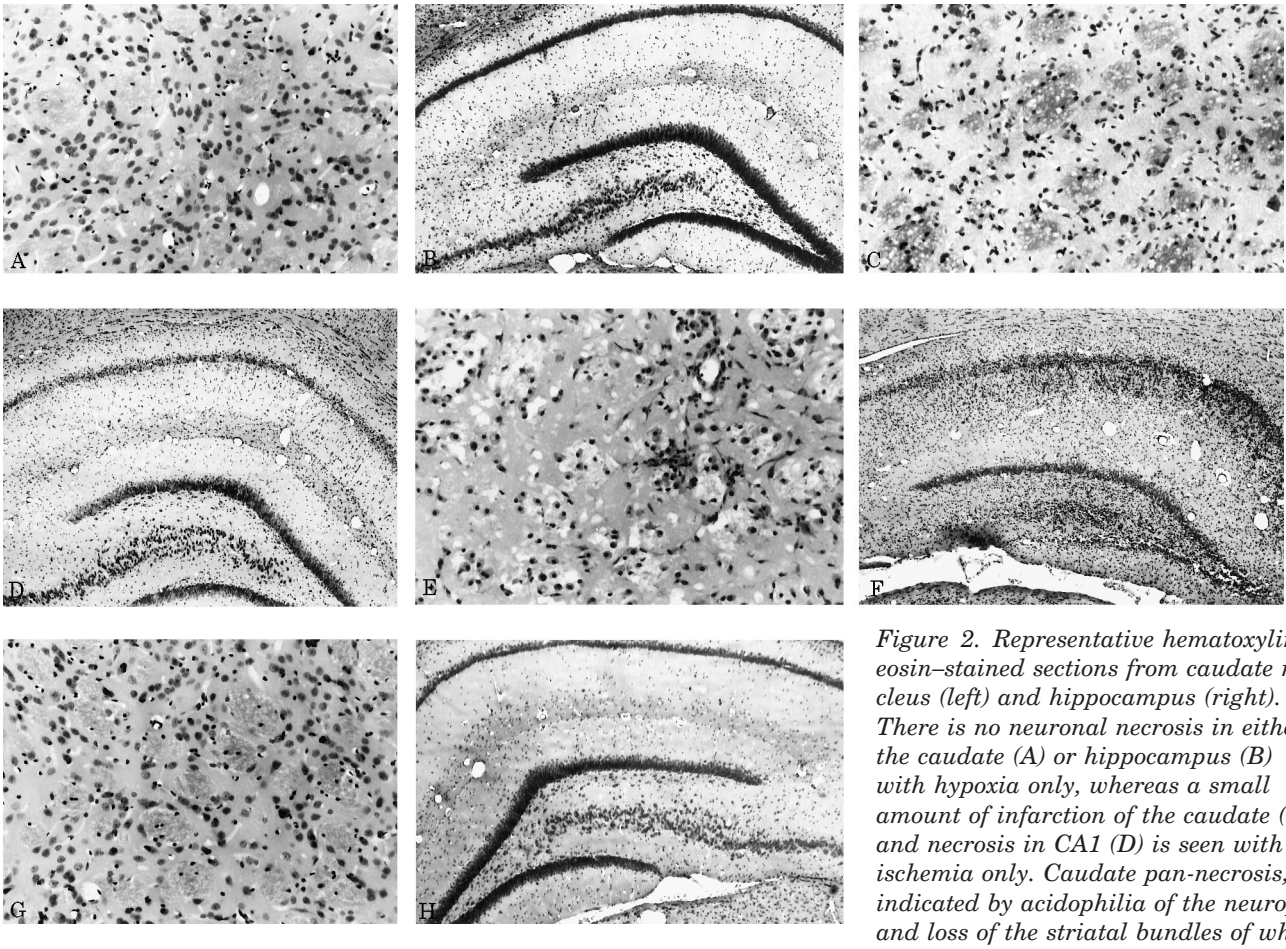

Figure 2. Representative hematoxylin-eosin–stained sections from caudate nucleus (left) and hippocampus (right). There is no neuronal necrosis in either the caudate (A) or hippocampus (B) with hypoxia only, whereas a small amount of infarction of the caudate (C) and necrosis in CA1 (D) is seen with ischemia only. Caudate pan-necrosis, indicated by acidophilia of the neuropil and loss of the striatal bundles of white matter (E), is seen with hypoxia plus ischemia, which also causes necrosis of all CA1 pyramidal neurons, CA3 pyramidal neurons, and the dentate gyrus (F). Many inflammatory cells infiltrate the hippocampus, but contralaterally in the same animal, no neuronal necrosis is seen in either striatum (G) or hippocampus (H). Bars = 250 μm.

oxia at PaO_2 levels <20 mm Hg owing to immediate cardiac death. Forty-four rats died within 2 days of the insult; 10 of these were in the hypoxia only group, where mortality was 43%. The rest were from hypoxia with ischemia groups, and died likely due to delayed cardiogenic shock[8] (5 of these 44 died following crescendo seizures). In the variable ischemia groups, at a fixed PaO_2 of 25 mm Hg, the mortality was 0%, 9%, 47%, 36%, and 53% at MABP 70, 60, 50, 40, and 30 mm Hg, respectively. In the groups with a fixed MABP of 30 mm Hg, the mortality was 29%, 18%, and 17% at PaO_2 > 100, 45, and 35 mm Hg, respectively.

Physiologic variables are shown in table 1. MABP was well controlled to the desired values by adjusting the FiO_2. The PaO_2 levels during control of MABP and the duration of hypoxia showed no differences among groups.

Hypoxia of PaO_2 = 25 mm Hg, despite the concurrent BP of 30 mm Hg, caused some slowing of EEG frequencies with increased amplitude (see figure 1), but failed to cause necrosis in any of 13 animals (figure 2). However, necrosis in the cortex, striatum, and hippocampus was seen in all hypoxia plus ischemia groups, and of 12 rats with ischemia only, 4 had brain damage (see figure 2). No necrotic neurons were found in any nonischemic hemisphere, even those contralateral to hemispheres severely damaged by hypotensive ischemia and severe hypoxia (see figure 2).

The degree of ischemic brain damage at a clamped level of hypoxia (PaO_2 = 25 mm Hg) was strongly influenced by BP, increasing in a linear fashion as MABP was lowered in steps through 70, 60, 50, 40, and 30 mm Hg, respectively (figure 3). Although no hemispheric tissue loss (cortical/subcortical pan-necrosis or atrophy) was seen at 70 mm Hg, hippocampal CA1 necrosis was already seen at this BP, confirming that neurons of the hippocampus are the most sensitive within the cerebral hemisphere.

The degree of hypoxia at a clamped BP influenced brain damage less clearly. At a fixed MABP of 30 mm Hg, the percentage of hemispheric tissue loss generally increased, but not always in a clear linear way, as the PaO_2 was lowered from >100 to 45, 35, and 25 mm Hg (see figure 3). Common carotid artery ligation caused hemispheric pan-necrosis and CA1 neuronal necrosis even at PaO_2 >100 mm Hg, and both were augmented by hypoxia, the results achieving significance at PaO_2 = 25 mm Hg (see figure 3). Cortical necrosis proved most sensitive to PaO_2, being eliminated entirely (see figure 3) at arterial oxygen tensions above 100 mm Hg.

Autoradiographic measurement of CBF. Carotid ligation led to a drop in ipsilateral CBF to the range of 15 to 35 mL/100 g/minute in most brain structures (for supplementary data, please visit our website at www.neurology.org and access the data through the Table of Contents page of the issue). Contralateral to the ligation, at a MABP of 30 mm Hg, CBF values were similar to those in the hypoxia only group at this same BP. Hypoxic hypotension to a

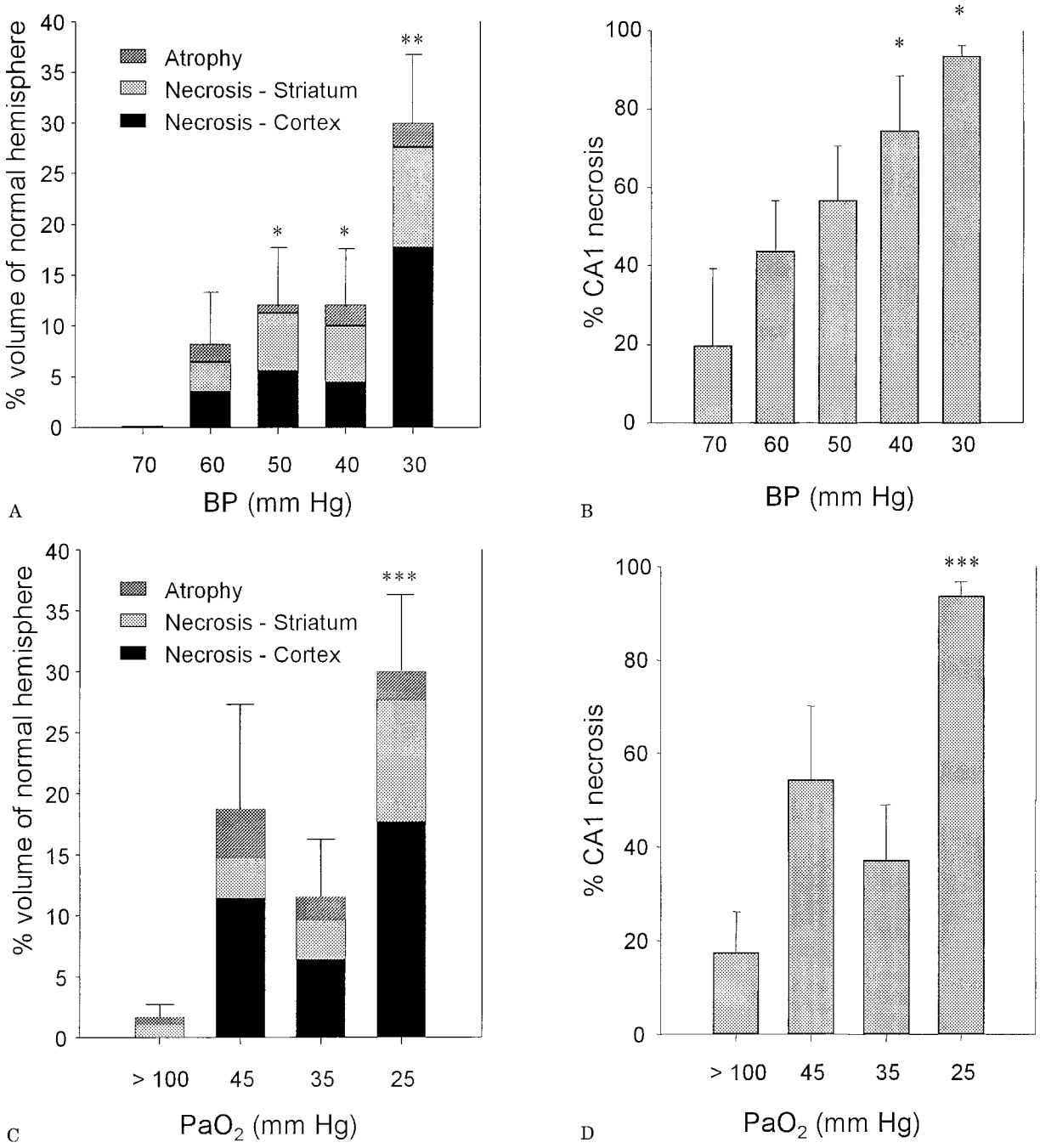

*Figure 3. Quantitated necrosis at graded levels of mean arterial blood pressure (MABP) with fixed PaO_2 = 25 mm Hg in the cerebral hemisphere (A) and the CA1 pyramidal cells (B). At a fixed MABP = 30 mm Hg, quantitated necrosis is shown in the hemisphere (C) and the CA1 pyramidal neurons (D) at graded levels of PaO_2. Total brain damage increased with reduction of MABP (A) and PaO_2 (B), the effect of hypotension being more clearly graded than hypoxia. Necrotic volumes were traceable because of the characteristically sharp demarcation of ischemic necrosis (see figure 6). Hemispheric volumes were calculated by integrating the coronal planar areas in the anteroposterior dimension. Atrophy represents nontraceable tissue lost, obtained by subtracting the ipsilateral from the contralateral hemisphere. The volume of tissue loss is referenced to the contralateral hemispheric volume (see text) to give the percentage of normal hemisphere damaged. *p < 0.05 and **p < 0.005 versus MABP 70 mm Hg group, ***p = 0.0001 versus PaO_2 > 100 mm Hg group.*

MABP of 30 mm Hg led to CBF values lower than normoxic animals at a MABP of 110 mm Hg. With carotid ligation, the addition of hypoxia to ischemia led to a further fall in local CBF in all brain regions. Global CBF in the hemisphere showed no evidence of hypoxic vasodilatation, but was reduced by hypoxia superimposed on ischemia, and to a lesser degree by the ischemic procedure alone (figure 4).

Transient MCA occlusion. Physiologic measures (table 3), apart from arterial oxygen tensions, were the same between groups. Hypoxia, as predicted from the Levine experiments, worsened ischemic brain damage after MCA

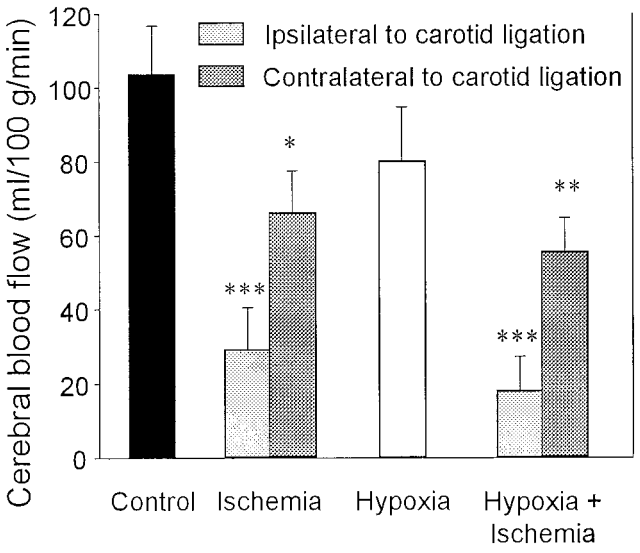

*Figure 4. Global hemispheric cerebral blood flow (CBF) values calculated as arithmetic means of all structures measured. Hypoxia with hypotension to 30 mm Hg shows reduced blood flow from controls. Hemispheric blood flow ipsilateral to carotid occlusion is depressed, with no increase in CBF with superadded hypoxia, at the same blood pressure. Mean ± SEM. ***p = 0.0001, **p = 0.01, *p = 0.05 versus control.*

occlusion to 24.31 ± 4.67% from 16.57 ± 6.98% of the hemisphere with normoxia (figure 5). Normobaric hyperoxia, on the other hand, protected the brain from ischemic injury, with only 7.50 ± 1.86% hemispheric damage (see figure 5). Hyperoxic protection in the cerebral cortex was remarkable, cortical necrosis being almost completely abolished (figure 6).

***Table 3** Physiologic variables in the middle cerebral artery occlusion study*

Variable	Normoxia	Hypoxia	Hyperoxia
Preischemia			
MABP (mm Hg)	89.6 ± 5.3	81.4 ± 1.8	85.4 ± 2.7
PaO_2 (mm Hg)	124.7 ± 4.8	125.0 ± 7.8	129.4 ± 5.5
$PaCO_2$ (mm Hg)	31.7 ± 1.9	37.3 ± 1.6	35.6 ± 1.4
pH	7.37 ± 0.02	7.38 ± 0.01	7.38 ± 0.02
Hematocrit (%)	45.5 ± 0.8	45.2 ± 1.1	45.3 ± 1.1
Glucose (mM)	7.7 ± 0.6	8.0 ± 0.8	8.0 ± 0.7
Intraischemia			
MABP (mm Hg)	62.4 ± 0.5	60.0 ± 0.8	61.6 ± 0.8
PaO_2 (mm Hg)	120.5 ± 4.1	46.5 ± 1.4*	213.9 ± 5.8*
$PaCO_2$ (mm Hg)	34.1 ± 2.2	39.8 ± 1.4	35.5 ± 0.8
pH	7.34 ± 0.02	7.31 ± 0.01	7.34 ± 0.02
Postischemia			
MABP (mm Hg)	92.1 ± 2.0	91.9 ± 1.8	88.1 ± 2.2
PaO_2 (mm Hg)	129.7 ± 4.0	130.2 ± 6.2	126.0 ± 4.5
$PaCO_2$ (mm Hg)	40.5 ± 2.2	40.9 ± 1.6	42.9 ± 1.5
pH	7.30 ± 0.02	7.33 ± 0.01	7.31 ± 0.01
Hematocrit (%)	45.3 ± 1.1	45.6 ± 1.1	44.2 ± 1.0
Glucose (mM)	7.7 ± 0.6	8.1 ± 1.0	7.8 ± 0.3

Values are mean ± SEM. *p* Values derived from one-way ANOVA followed by Scheffé test.

* $p < 0.001$ Compared with normoxia group.

MABP = mean arterial blood pressure.

Discussion. Early experimental studies of hypoxia used immersion in 100% gaseous nitrogen to produce hypoxic hypoxia combined with carotid ligation in the Levine model.[18] Although this produced cerebral necrosis, and the animals were indeed exposed to a hypoxic atmosphere, ischemia undoubtedly contributed as an unmonitored variable. Our first aim, therefore, was to use a Levine type of experimental model with complete physiologic monitoring to study the interaction of hypoxia and ischemia, and to test the hypothesis that severe hypoxia alone is capable of damaging the brain. Despite a pure hypoxic insult that was close to the lethal level (indicated by the 43% mortality of the hypoxia only group), no survivors showed brain necrosis. We thus demonstrate that a severe insult of pure hypoxia, nearly lethal in severity, does not cause brain damage. Our finding of no necrosis contralateral to the most severely damaged hemispheres in the separate ischemia plus hypoxia series lends further support to the notion that hypoxia alone does not cause brain necrosis.

Our findings confirm earlier assertions that hypoxia does not cause brain damage.[9,19] Clinically well documented cases exist of remarkable and complete neurologic recovery following up to 2 weeks of coma related to hypoxia without cardiac arrest.[2,3] Autopsy in such cases of profound, pure hypoxia, with neurologic recovery but death from other causes, has shown no necrosis in the brain.[4] The reasons likely relate to hypoxia-induced alterations at the neurochemical and synaptic levels, without irreversible damage at the level of the neuronal perikaryon (selective neuronal necrosis) or tissue (infarction or pan-necrosis). Clinically, in cases of coma, it thus becomes paramount for prognostic purposes to distinguish between cardiorespiratory arrest and pure respiratory arrest without cardiac arrest or cardiogenic shock. The prognosis is good in the latter, but guarded if global ischemia has occurred, due to the presence of cortical necrosis.[20]

Pure hypoxia might be relatively innocuous to the brain of the intact organism owing to several protective mechanisms. Total and regional CBF increases progressively with reduction in PaO_2 if BP is maintained.[5,21] This hypoxic increase in CBF maintains not only the delivery of oxygen,[22,23] but also the removal of waste products such as lactate and hydrogen ions, themselves capable of causing brain damage.[24] Although there is increased carbohydrate metabolism and lactate generation through anaerobic glycolysis hypoxia,[6,25] this is mild, and unaccompanied by depletion of cerebral adenosine triphosphate (ATP) reserves, even at PaO_2 levels of 25 mm Hg.[25-27]

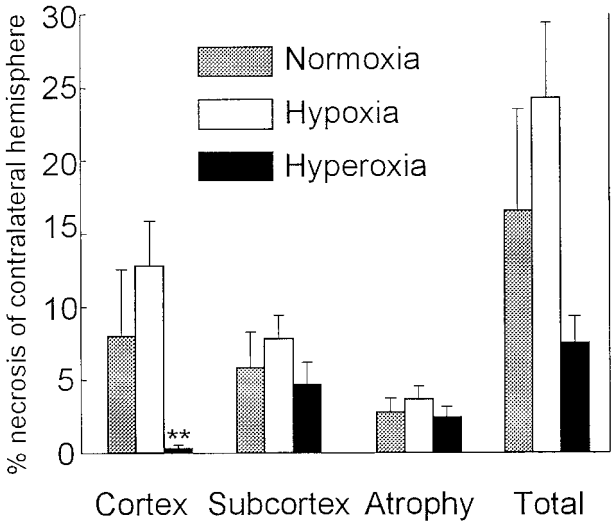

*Figure 5. Quantitated necrosis in cortex and striatum, as well as atrophy and total brain damage (sum of necrosis and atrophy), normalized to the contralateral hemisphere. Deep gray matter receives marginal benefit from high oxygen tensions, but cortical necrosis is all but eliminated (0.34 ± 0.22% with hyperoxia, 7.97 ± 4.63% with normoxia, and 12.82 ± 3.08% with hypoxia). **$p < 0.01$, ANOVA on arcsine-transformed percentage data.*

This essential difference between ischemia and hypoxia may be of fundamental importance in the genesis of brain necrosis. Hypoxia leaves autoregulation of blood flow intact until PaO_2 drops below 25 mm Hg for several minutes,[5] a point at which cardiac function becomes severely impaired. Hypoxia accelerates anaerobic glycolysis and lactic acidosis early, even before ATP depletion occurs.[27-29] These minimal perturbations in brain energy metabolism probably also explain why EEG show minimal changes due to profound hypoxia in humans[6,30,31] and animals.[32]

The pathogenesis of hypoxic coma and Lance-Adams syndrome must be considered, if pure hypoxia causes no brain necrosis. Hypoxic coma is likely explained at the synaptic level. A purely hypoxic insult does not damage neurons,[33] but damages synapses selectively.[34,35] Furthermore, selective GABAergic deficiency results.[35,36] The deficit of GABA explains the hypoxic tendency to seizures and myoclonus,[37,38] GABAergic synapses being damaged selectively over non-GABAergic ones.[35] Synaptic hypoxic alterations occur without causing necrosis at the cell or tissue level. It is important not to confuse the seizure tendency after hypoxia[1] with that following cardiac arrest, which carries a poor prognosis.[37,38] The time course of recovery from purely hypoxic coma is consonant with the time course of synaptic regeneration and repair, being in the order of 2 weeks.[2-4]

With regard to hyperoxia, at hyperbaric pressures, hyperoxia produces brain necrosis by the production of oxygen-derived free radicals. Newborn rats[13] are more vulnerable than adult rats, in which hyperbaric pressures are required to produce hyperoxic damage.[14,39] The result of unilateral carotid occlusion is

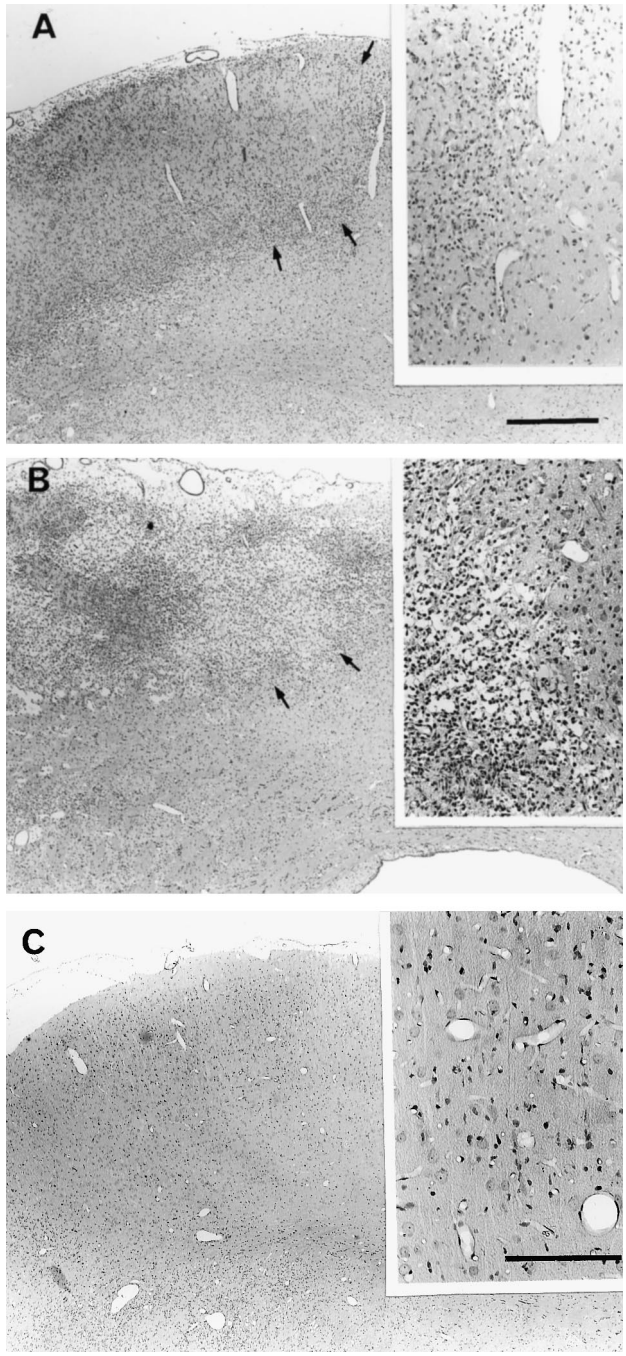

Figure 6. Representative hematoxylin-eosin–stained sections from middle cerebral artery (MCA) occlusion experiments show how arterial oxygen levels influence MCA infarction in the cerebral cortex. Normoxia (A) (PaO_2 = 120.5 ± 4.1 mm Hg) produces a smaller infarct than hypoxia (B) (PaO_2 = 46.5 ± 1.4 mm Hg), which produces a large infarct with a richer neutrophilic infiltration. Hyperoxia (C) (PaO_2 = 213.9 ± 5.8 mm Hg) converts the infarct into selective neuronal necrosis (inset), visible as microglial rod cells (dendritic phagocytosis) and acidophilic neuronal perikarya. There is no traceable pan-necrosis. The characteristic sharp border (arrows) of cerebral infarction, which allows quantification, is seen in the normoxic and hypoxic rats. Scale bar = 500 μm (inset, 150 μm).

heuristic in hyperoxic brain damage: the hemisphere supplied by the unobstructed artery shows necrosis, but the hemisphere ipsilateral to the ligated carotid artery is protected from necrosis by the occlusion.[39] Several experimental reports show therapeutic promise for hyperbaric oxygenation in global ischemia.[40-42] Normobaric hyperoxygenation is clinically more practical than the use of a hyperbaric chamber. It is thus noteworthy that we found reductions in cortical ischemic necrosis at normal atmospheric pressure.

Concerns have been raised over oxygen toxicity in the reperfusion period after global ischemia,[43] but other experiments have shown that oxygen-derived free radical production is not increased with hyperoxia in the reperfusion period.[44] We show here in both the Levine preparation and the MCA occlusion model, two essentially focal models, that arterial blood oxygen levels strongly influence ischemic brain damage. Perhaps most importantly, necrosis in the cerebral cortex is especially sensitive to arterial blood oxygenation, and can be mitigated in this focal rat model by PaO_2 levels of just over 200 mm Hg, a range that could be attained clinically.

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Stroke in children

The coexistence of multiple risk factors predicts poor outcome

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Article abstract—*Objective:* To characterize the risk factors for stroke in children and their relationship to outcomes. *Methods:* We reviewed charts of children with ischemic and hemorrhagic stroke seen at Hôpital Sainte-Justine, Montréal between 1991 and 1997. *Results:* We found 51 ischemic strokes: 46 arterial and 5 sinovenous thromboses. Risk factors were variable and multiple in 12 (24%) of the 51 ischemic strokes. Ischemic stroke recurred in 3 (8%) patients with a single or no identified risk factor and in 5 (42%) of 12 patients with multiple risk factors ($p = 0.01$). We also found 21 hemorrhagic strokes, 14 (67%) of which were caused by vascular abnormalities. No patient with hemorrhagic stroke had multiple risk factors. Hemorrhagic stroke recurred in two patients (10%). Outcome in all 72 stroke patients was as follows: asymptomatic, 36%; symptomatic epilepsy or persistent neurologic deficit, 45%; and death, 20%. Death occurred more frequently in patients with recurrent stroke (40%) than in those with nonrecurrent stroke (16%). *Conclusions:* Multiple risk factors are found in many ischemic strokes and may predict stroke recurrence. Recurrent stroke tends to increase rate of mortality. Because of the high prevalence and importance of multiple risk factors, a complete investigation, including hematologic and metabolic studies and angiography, should be considered in every child with ischemic stroke, even when a cause is known. **Key words:** Children—Stroke—Outcome—Risk factor—Investigation.

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Childhood stroke affects 2.7 per 100,000 children per year[1] and is known to recur in up to 20%.[2] In individual children with stroke, the extent of investigations for risk factors often is limited, especially when an obvious cause is known. However, multiple risk factors may coexist in childhood stroke,[3] and their detection in individual patients can modify the prognosis and medical treatment. We reviewed the charts of children with ischemic and hemorrhagic stroke seen at our center between 1991 and 1997. Our objective was to characterize the stroke risk factors and their relationship to outcomes.

Methods. *Patients.* We defined stroke as a focal neurologic deficit of sudden onset, not solely related to seizure, resulting from irreversible focal ischemic (ischemic stroke) or hemorrhagic (hemorrhagic stroke) damage to the brain parenchyma secondary to a cerebrovascular disorder. Ischemic stroke included arterial ischemic stroke and sinovenous thrombosis. We searched patient charts at a single children's health care center (Hôpital Sainte-Justine), using ICD-9 codes, to identify all patients age 1 month to 18 years diagnosed with stroke from 1991 to 1997. We excluded traumatic hemorrhages but included children with ischemic stroke related to trauma. Unless accompanied by cerebral hemorrhage or infarct, patients with sinovenous thrombosis or with extracerebral intracranial bleeding (e.g., epidural and subdural hematomas, and subarachnoid hemorrhage) were excluded. We also excluded mitochondrial disorders because stroke-like episodes in these conditions are not clearly ischemic.[4]

Data collection. The study neurologist (S.L.) reviewed the charts of patients who met the inclusion criteria. Data collected regarding stroke risk factors were ethnic origin, family history of thrombosis, medications, recreational drug use, infection or head trauma in the 4 weeks preceding stroke, headache, and associated systemic diseases. Table 1 lists the radiographic and laboratory investigations reviewed for each case. The presence of anticardiolipin antibody (aCLA) was defined as a significantly elevated immunoglobulin M (IgM) or IgG titer. Risk factors were classified into four categories: vascular abnormali-

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Table 1 *Radiographic and laboratory investigations reviewed in our series*

Type of testing or screening	Tests performed
Metabolic	Blood glucose
	Blood electrolytes, urea nitrogen, and creatinine
	C-reactive protein level
	Plasma homocysteine and screening for other amino and organic acids
	Enzymatic activity and thermolability of the methylene tetrahydrofolate reductase
	Cholesterol and triglyceride studies
	Blood and CSF lactate and pyruvate levels
Hematologic	Complete blood count and differential
	Hematocrit and hemoglobin level
	Hemoglobin electrophoresis
	Erythrocyte sedimentation rate
	Prothrombin time and activated partial thromboplastin time
	Blood levels of protein S, protein C, antithrombin, and coagulation factors
	Anticoagulant response to activated protein C
	Coagulation studies for lupus anticoagulant
Toxicologic	Toxicologic screening tests
Immunologic	Anticardiolipin and antinuclear antibodies
	Venereal disease research and rheumatoid factor laboratory
	C3 and C4 complement protein levels
Genetic	G20210A point mutation of the *prothrombin* gene
	G1691A point mutation of the blood coagulation *factor V* gene (factor V Leiden)
	C677T point mutation of the *methylene tetrahydrofolate reductase* gene
Cerebral imaging and cerebrovascular	CT of the brain
	MRI of the brain
	SPECT
	Carotidovertebral and transcranial Doppler ultrasonography
	Conventional cerebral angiography
	MR angiography
Cardiac	EKG and 24-hour Holter monitoring
	Transthoracic and transesophageal echocardiography

ties, hematologic and metabolic disorders, cardiac disorders, and other risk factors. Outcomes at the time of discharge or last follow-up visit were classified into five categories: asymptomatic, symptomatic epilepsy, persistent neurologic deficit, recurrent stroke, and death.

Statistical analysis. Using Fisher's exact test, we compared stroke recurrence between patients with multiple risk factors and patients with a single or no identified risk factor. We also compared death between the same two groups of patients. Finally, we compared death between patients with recurrent strokes and patients with a single episode of stroke.

Results. *Patients.* Our chart review identified 330 possible patients with stroke, 72 of whom met our criteria and formed our final cohort for analysis. Reasons for exclusion were age younger than 1 month or older than 18 years (n = 77); traumatic hemorrhage (n = 118); extracerebral intracranial bleeding without cerebral damage (n = 54); incomplete chart (n = 5); and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (n = 4).

We found 51 children with ischemic stroke, including 46 with arterial ischemic stroke and 5 with sinovenous thrombosis, and 21 children with hemorrhagic stroke. The racial background of these 72 patients was white (85%), black (6%), Arabic (6%), and Asian (3%). The male–female ratio was 1.5:1. Mean age at diagnosis was 6.1 years for arterial ischemic strokes, 9.1 years for sinovenous thromboses, and 7.9 years for hemorrhagic strokes. The distribution of strokes according to age group and category of risk factor is shown in table 2. Among our patients with arterial ischemic stroke, only seven were older than 12 years and younger than 18 years. Strokes tended to occur before age 5 years in children with cardiac disorders, moyamoya (mean age, 3.4 years), and multiple risk factors. In contrast, strokes tended to occur at older ages in children with other vascular disorders. In patients with recurrent stroke, the mean age at the first episode was 5.5 years (range 0.4 to 15.6 years).

Investigations. In the 72 stroke patients, neuroimaging included brain CT scan alone in 41 (57%), brain MRI

Table 2 *Distribution of strokes according to age group, type of stroke, and risk factor category*

	Type of risk factor by type of stroke*						
Age	None	Vasc only	Hem only	Cardi only	Other	Mult	Total
1 mo–5 y	3/0/1	4/0/5	1/0/2	4/0/0	3/1/0	9/0/0	24/1/8
>5–12 y	3/0/1	8/0/4	1/2/0	1/0/0	0/0/1	2/1/0	15/3/6
>12–18 y	2/0/1	2/0/5	0/0/0	1/0/0	2/1/1	0/0/0	7/1/7
Total	8/0/3	14/0/14	2/2/2	6/0/0	5/2/2	11/1/0	46/5/21

* Values represent no. of arterial ischemic stroke/sinovenous thrombosis/hemorrhagic stroke, respectively.

Vasc = vascular abnormalities; Hem = hematologic or metabolic disorders; Cardi = cardiac disorders; Mult = multiple risk factors.

alone in 3 (4%), and both studies in 27 (38%). Only one patient, who was diagnosed at autopsy, had neither study done. Among the 51 patients with ischemic stroke, 34 patients (67%) underwent conventional cerebral angiography, including 6 of 8 patients with no identified risk factor. Six patients (12%) underwent MR angiography, and 11 patients (22%) had no vascular imaging studies. Among the 21 patients with hemorrhagic stroke, 15 patients (71%) underwent conventional cerebral angiography, including 2 of 3 patients with no identified risk factor. None had MR angiography. Six patients (29%) had no vascular imaging studies. Transthoracic or transesophageal echocardiographies were performed in 36 patients (71%) with ischemic stroke and 7 (33%) with hemorrhagic stroke. Among the 51 children with ischemic stroke, prothrombotic testing included protein C, protein S, and antithrombin levels in 38 patients (75%); the presence of an antiphospholipid (aPL) antibody (including aCLA and lupus anticoagulant) in 37 patients (73%); activated protein C resistance (aPCR) or factor V Leiden mutation in 15 patients (29%); plasma homocysteine level in 9 patients (18%); the presence of the mutant C677T methylene tetrahydrofolate reductase (*MTHFR*) gene in 3 patients (6%); and the presence of the mutant G20210A *prothrombin* gene in 1 patient (2%).

Stroke risk factors. The risk factors identified in each of the three stroke types (arterial ischemic stroke, sinovenous thrombosis, and hemorrhagic stroke) are summarized in table 3.

Arterial ischemic stroke. In the 46 children with arterial ischemic stroke, hematologic or metabolic disorders were identified in 9 (20%), and 7 of these had multiple risk factors. The presence of aCLA (n = 3) was the most frequent prothrombotic condition observed in our series. Hyperhomocysteinemia was found in one child who was homozygous for C677T point mutation of the *MTHFR* gene. This child also had renal failure, hypercholesterolemia, and folate deficiency.

A cardiac disorder was present in 9 (20%) of 46 patients. Six of these children had cyanotic congenital heart disease, including one child with trisomy 21 and another with pulmonary artery stenosis and a patent foramen ovale. In three children with cyanotic congenital heart disease, the stroke occurred in the context of polycythemia (n = 2) or cardiac surgery (n = 1).

Primary vascular disorders were present in 11 (31%) of the 36 patients with arterial ischemic stroke who underwent conventional or MR angiography. In 6 (17%), a moyamoya pattern was identified. All children with moyamoya were white. Of the six moyamoya patients, one had trisomy 21 with congenital heart disease and polycythemia, another had trisomy 21 and aCLA, and a third had aCLA.

We found nonspecific arteriographic changes in a further 10 (24%) of the 36 patients with arterial ischemic stroke who underwent angiography. Clinical or laboratory findings did not suggest a specific cause in these patients. In particular, a history of varicella was absent. The arteriographic abnormalities were localized to the proximal portion of the large intracranial arteries (n = 7) or to the distal portion (n = 3). These abnormalities consisted of single stenosis (n = 3), multiple unilateral stenoses (n = 5), and multiple bilateral stenoses (n = 2). At the site of the stenoses, no specific signs of dissection were noted, including no intimal flap, double lumen, or string signs. MRI showed no sign of methemoglobin within the arterial wall. Nonspecific changes on arteriography were present in all three patients with arterial ischemic stroke who had had a nonspecific upper respiratory infection within the preceding 4 weeks.

In ischemic stroke patients, three had extrinsic arterial compression caused by underlying expanding processes, including subarachnoid hemorrhage with a large intracranial hematoma (n = 1), subdural hematoma (n = 1), and diffuse brain edema secondary to acute liver failure with transtentorial herniation and compression on posterior cerebral artery (n = 1).

Sinovenous thrombosis. Risk factors were found in all five patients with sinovenous thrombosis. Two patients had a nonspecific infection. Three children had a hematologic or metabolic disorder, including one with nephrotic syndrome and dehydration.

Hemorrhagic stroke. Among the 21 patients with hemorrhagic stroke, risk factors included vascular abnormalities in 14 patients (67%), hematologic disorder in 2 patients (10%), and bleeding into an intracranial tumor in 2 patients (10%). In 3 (14%) of the 21 patients, no risk factor was identified. No patient with hemorrhagic stroke had multiple risk factors.

Outcome. The overall outcome in our cohort is presented in tables 4 and 5. Fourteen patients (20%) died. For another 6 (8%) patients, the outcome was available only at the time of discharge. The median length of the follow-up period for the remaining 52 patients (72%) was 1.9 years (range 0.25 to 7.2 years). Thirty-five percent of patients with ischemic strokes and 38% of those with hemorrhagic strokes were asymptomatic, whereas 49% of patients with ischemic strokes and 33% of those with hemorrhagic strokes had symptomatic epilepsy or persistent neurologic deficit (see table 4).

Table 3 *Risk factors for types of stroke*

Arterial ischemic		Sinovenous thrombosis		Hemorrhagic	
Risk factor	n	Risk factor	n	Risk factor	n
Vascular abnormalities					
NS arteriographic changes	10	None	0	Arteriovenous malformations	8
Moyamoya				Cavernous hemangioma	4
Primary	4				
Secondary to trisomy 21	2				
Isolated angiitis of the CNS	2			Venous malformation	1
Fibromuscular dysplasia	1			Ruptured intracranial aneurysm	1
Lupic vasculopathy	1				
Spontaneous arterial dissection	1				
Hematologic and metabolic disorders					
Anticardiolipin antibodies	3	Nephrotic syndrome	1	Coagulopathy (liver failure)	1
Secondary polycythemia	2	Crohn's disease	1	Hypofibrinogenemia	1
Hemoglobinopathy SC	1	L-Asparaginase	1		
Factor V Leiden mutation	1				
Protein S deficiency	1				
Hemolytic–uremic syndrome	1				
Hyperhomocysteinemia	1				
Hypercholesterolemia	1				
Cardiac disorders					
Congenital heart disease	6	None	0	None	0
Cardiac surgery	1				
Acquired heart failure					
Myocardiac toxicity (Adriamycin [doxorubicin])	1				
Viral myocarditis	1				
Endocarditis	1				
Other causes					
NS infection	3	NS infection	2	Intracranial tumor bleeding	2
Extrinsic arterial compression	3	Dehydration	1		0
Pneumonia (septic embolisms)	1				
Hypovolemic shock	1				0
No risk factor	8		0		3
Multiple risk factors*	11		1		0
Total	46		5		21

* Patients with stroke associated with multiple risk factors are represented more than once.

NS = nonspecific.

Stroke recurrence. Ischemic stroke recurred in 5 (42%) of 12 patients with multiple risk factors and in 3 (8%) of 39 patients with a single or no identified risk factor. This difference was statistically significant ($p = 0.01$, Fisher's exact test). At least one prothrombotic condition was present in all five patients with multiple risk factors and stroke recurrence. The following combinations of risk factors were noted in these five children: moyamoya associated with trisomy 21, cyanotic congenital heart disease, and polycythemia (n = 1); cyanotic congenital heart disease and polycythemia (n = 1); moyamoya associated with trisomy 21 and aCLA (n = 1); protein S deficiency and aCLA (n = 1); and hyperhomocysteinemia and hypercholesterolemia (n = 1). Among the three patients with recurrent ischemic stroke and a single or no identified risk factor, one child had a tyrosine kinase deficiency with nonspecific arteriographic changes, another child had Crohn's disease and two episodes of sinovenous thrombosis, and the third patient had three episodes of ischemic stroke with no identified risk factor. In our series, 2 (10%) of 21 hemorrhagic strokes recurred; both were caused by complex vascular malformations not amenable to surgery.

Death. Death was more frequent in children with hemorrhagic stroke (29%) than in ischemic stroke (16%). Death occurred in 4 (40%) of the 10 children with recurrent hemor-

Table 4 *Outcome of stroke according to stroke type and presence of risk factors*

	Ischemic stroke							Hemorrhagic stroke		
Outcome	None	Vasc only	Hem only	Cardi only	Other	Mult	Total (%)	None	Single	Total (%)
Asymp	3	5	2*	2	2*	4	18 (35)	3	5	8 (38)
Ep	1	0	0	0	0	1	2 (4)	0	1	1 (5)
ND	4	7	2	1	2	3	19 (37)	0	5	5 (24)
Ep/ND	0	1	0	1	1*	1*	4 (8)	0	1	1 (5)
Death	0	1	0	2	2	3*	8 (16)	0	6	6 (29)
Total	8	15	3	6	7	12	51 (100)	3	18	21 (100)
Recurr	1	1	1	0	0	5	8 (16)	0	2	2 (10)

Values are number of patients with risk factors for the stroke types.

* Individuals with sinovenous strokes (n = 5).

Asymp = asymptomatic; Vasc = vascular abnormalities; Hem = hematologic or metabolic disorders; Cardi = cardiac disorders; Mult = multiple risk factors; Ep = symptomatic epilepsy; ND = persistent neurologic deficit; Recurr = recurrent stroke.

rhagic or ischemic stroke and in 10 (16%) of the 62 children with a single episode of stroke. Deaths resulted from complications of stroke (n = 11), underlying cardiac disorders (n = 2), and acute respiratory distress syndrome (n = 1).

Discussion. *Patients.* Previous studies[5,6] report that about 45% of strokes occur before the age of 5 years. This agrees with our findings. The slight predominance of male patients in our series also is consistent with previous studies,[3,6,7] which report male–female ratios of 1:1 to 1.2:1. The frequency of moyamoya in our cohort is similar to that of the large non-Japanese series,[7] which reports the disorder in up to 10% of children with ischemic stroke. Our low proportion of black patients accounts for our finding only one case of hemoglobinopathy.

Investigations. During the study intervals, our center followed the usual approach, in which investigation of children with stroke is selective and guided by clinical suspicion. Therefore, investigations were not uniform in our retrospective series. Hyperhomocysteinemia and mutant C677T *MTHFR*, aPCR and G1691A *factor V* gene, and G20210A *prothrombin* gene, which have been identified recently, were investigated in few of our patients. Because many children in our series (76%) underwent angiographic evaluation, our study provides a realistic estimate of the prevalence of vascular disorders in children with stroke.

Stroke risk factors. Few (15%) of our patients had no identified stroke risk factor. Our results are similar to those of other recent studies, in which no etiology was found in 20% to 36%[7,8] of patients with ischemic stroke and in 11%[1] of patients with hemorrhagic stroke.

Hematologic and metabolic disorders. Despite the absence of systematic screening in our cohort, we found at least one hematologic or metabolic disorder in about 25% of ischemic stroke patients. Prothrombotic disorders also were frequent in a recent series,[3] being associated with 35 (38%) of 92 pediatric ischemic strokes. We have shown that hematologic and metabolic disorders are frequently found in combination with other risk factors in patients with ischemic stroke. The presence of multiple risk factors has been previously reported to increase the risk of thrombosis considerably.[9] Based on these observations, we believe that an extensive hematologic and metabolic screening must be part of the workup of pediatric ischemic strokes, even when a cause

Table 5 *Outcome of stroke according to number of episodes and stroke type*

	Single episode of stroke (n = 62)			Recurrent stroke (n = 10)		
Outcome	Ischem	Hemorr	Total (%)	Ischem	Hemorr	Total (%)
Asymp	16	8	24 (39)	2*	0	2 (20)
Ep	1	1	2 (3)	1	0	1 (10)
ND	18	4	22 (35)	1	1	2 (20)
Ep/ND	3	1	4 (6)	1	0	1 (10)
Death	5	5	10 (16)	3	1	4 (40)

* The single case of sinovenous thrombosis.

Ischem = arterial ischemic stroke; Hemorr = hemorrhagic stroke; Asymp = asymptomatic; Ep = symptomatic epilepsy; ND = persistent neurologic deficit.

is known. Arterial ischemic strokes should be investigated as thoroughly as sinovenous thromboses, ruling out the presence of aPL antibodies and deficiencies in protein C, protein S, and antithrombin, as well as aPCR (or factor V Leiden) and hyperhomocysteinemia (or C677T *MTHFR* gene mutation). Although a recent study reports that 20% of patients with sinovenous thrombosis were heterozygous carriers of the G20210A *prothrombin* gene point mutation,[10] the relative importance of this mutation in patients with arterial ischemic stroke remains to be defined.[11] Sickle cell disease must be ruled out in black patients with stroke because a transfusion program prevents stroke recurrence.[12] Mitochondrial disorders also are important to exclude in patients presenting with sudden neurologic deficit.Cardiac disorders. Although echocardiography was not done for all patients in our series, we found a cardiac risk factor in about 20% of patients with ischemic stroke. In previous reports, up to 15% of ischemic strokes were attributed to cardiac disorders,[7,13] most frequently to congenital heart disease.[14] Therefore, cardiac evaluation remains essential in the investigation of any ischemic stroke, especially in younger children. Congenital heart disease tends to cause stroke during the first 4 years of life, often in the setting of cardiac surgery or catheterization.[14] Among our six patients with congenital heart disease, only one had a cardioembolic stroke associated with cardiac surgery. As found in our series, cyanotic congenital heart disease has been associated with moyamoya disease and polycythemia.[15] In children with congenital heart disease and ischemic stroke, these two associated conditions must be ruled out because such findings can modify therapeutic decisions.

Vascular abnormalities. A recent large series[7] found specific vasculopathies in 18% of pediatric ischemic strokes. We identified recognizable vasculopathies in almost 25% of our patients with arterial ischemic stroke. This percentage may underestimate their prevalence because not all patients in our series underwent vascular imaging. These findings underline the importance of vascular investigation in all arterial ischemic strokes in children. Moyamoya was the most frequent recognizable vasculopathy in our cases of ischemic stroke. Although the exact pathophysiologic mechanism of moyamoya remains unknown, it has been associated with many conditions, including trisomy 21 and congenital heart disease.[15,16] The association of moyamoya with lupus anticoagulant[17] or with a significantly elevated blood level of IgG aCLA[18,19] also has been reported, albeit rarely. We report here two more cases of moyamoya associated with aCLA and arterial ischemic stroke. Surprisingly, in our series, aCLA was found in 2 of 6 patients with moyamoya but in only 1 of 31 without moyamoya ($p = 0.06$). Despite the few patients in our series, this finding may suggest an association between aPL antibodies and moyamoya in children with arterial ischemic stroke, rather than only a rise in IgG aCLA as an epiphenomenon in response to an acute cerebral event. Although the link between aPL antibodies and thrombosis also remains unknown, vascular endothelium is believed to be a major target for the antibodies.[20] A direct cause–effect relationship cannot be established. However, a thrombogenic effect of aPL antibodies may induce chronic progressive occlusion of cerebral vessels, characteristically of the supraclinoid portion of the internal carotid arteries with telangiectatic vessel proliferation, a combination that constitutes the moyamoya pattern seen on angiography.[21] Alternatively, moyamoya may cause the remodeling of endothelial membrane phospholipids into a more immunogenic target, thereby triggering the synthesis of aPL antibodies. A third possibility is that both moyamoya and aPL antibodies result from a common underlying disorder and independently induce arterial ischemic stroke. Therefore, we believe that testing for aPL antibodies should be done in all children with ischemic stroke, and we agree with other investigators[19] that it is especially important in those with moyamoya.

We found nonspecific arteriographic changes in 10 (22%) of 46 children with arterial ischemic stroke. These changes were classified as nonspecific changes because no evidence for specific causes of vasculopathies was found in these patients. Abnormalities were more often multiple, unilateral, and localized proximally on the large intracranial arteries. Similar nonspecific changes have been reported in about 30% of a series[6] of 48 Japanese children with ischemic stroke. In that series, mild head trauma with mechanical vascular injury and vasospasm or vasculitis secondary to infection were proposed as causes. In children with arterial ischemic stroke, unexplained arterial stenosis at the circle of Willis (seen on angiograms) has been reported to be frequently spontaneously reversible.[22] Among our 46 cases of arterial ischemic stroke, a recent upper respiratory infection was found in 3 (30%) of 10 children with nonspecific arteriographic changes and in none of the 36 children without these changes. This finding suggests that, at least in some children, such changes are secondary to a concurrent or recent infection. Nonspecific infection of the head and neck that produces stimulation of the superior cervical ganglion could predispose cerebral vessels to inflammatory changes and thrombosis. This mechanism has been postulated in postvaricella angiopathy[23] and in moyamoya disease.[21] Nonspecific arteriographic changes could, in some cases, represent the earliest stages of moyamoya.

Vascular malformation and ruptured intracranial aneurysm were the principal causes of hemorrhagic stroke in our cohort. In one study[1] that included both intraparenchymal and extraparenchymal forms of intracranial hemorrhage, these two causes represented about two thirds of hemorrhagic strokes. We agree with other researchers[24] that angiography should be done in any spontaneous intracerebral hemorrhage in young patients.

Other risk factors. In our population, a recent nonspecific infection was found in about 10% of children with ischemic strokes. Another study[13] found

that a recent or concurrent infection, often affecting the respiratory system, occurred more frequently in children with ischemic stroke than in control subjects (34% versus 11%). Dehydration, secondary hypercoagulability, endothelial damage, altered lipid and prostaglandin metabolism, and secondary vasculitis all can be involved.[6,13] Infection is found less often in patients with hemorrhagic stroke.[25] We found no ischemic stroke associated with trauma and only one patient with spontaneous arterial dissection. In one study[7] of arterial ischemic stroke in the young, arterial dissection was present in none of 81 children younger than 15 years of age but in 3 of 11 children age 15 to 18 years. Our series included only 7 patients with arterial ischemic stroke age 12 to 18 years. This may explain our low frequency of arterial dissections. Recent or concurrent systemic or intracranial infection and mild head and neck trauma should not be overlooked as a stroke risk factor.

Outcome. Variability in length of follow-up and in inclusion/exclusion criteria may generate different cohorts and outcomes. Because MRI was not frequently done for stroke at our center during the study period, it is possible that children with stroke undetectable by CT scan went undiagnosed. Thus, our cohort may underrepresent milder strokes. However, in one large series[5] of children with stroke, the reported outcomes were similar to ours, including the complete resolution of initial deficits in 23% and death in 23%. In this series, all deaths were attributable to neurologic complications of stroke.[5] This also was the most frequent cause of death in our cohort. In our study, mortality was greater in hemorrhagic stroke, but neurologic outcomes were similar. A worse outcome for hemorrhagic strokes is observed.[5]

Stroke recurrence and death. Our stroke recurrence rate was similar to the 20% recurrence rate previously reported.[2] Recurrence has been linked to migraine,[13] metabolic disease,[15] moyamoya disease,[6] and sickle cell anemia.[12] In a series[14] of 50 strokes associated with congenital heart disease, the preliminary outcome was death in 8%, no residual symptoms in 40%, and recurrence in only 2%. We have shown that the presence of multiple stroke risk factors is frequent in children with ischemic stroke. We also have shown that recurrent strokes are significantly more likely in patients with multiple risk factors than in those with a single or no identified risk factor. We found a trend toward more frequent death in patients with recurrent stroke, but this association was not statistically significant ($p = 0.10$). Further studies should re-evaluate this possible association. Our findings provide a rationale for undertaking a vigorous search for every risk factor in every pediatric stroke patient. In particular, risk factors that are frequently found, including prothrombotic conditions, cardiac disorders, and vascular abnormalities, must be ruled out in every ischemic stroke patient, even when a precise cause already has been identified. Some combinations of risk factors may require a multifaceted therapeutic approach. In addition, less frequent risk factors also should be excluded, if clinically suspected, when a stroke remains unexplained and when stroke recurs.

Additional predictors of outcome were not analyzed in our series. Such analyses should be carried out in future studies because prediction of outcome influences the aggressiveness of therapy and rehabilitation and clarifies the prognosis. With our improved understanding of cerebrovascular diseases and the wide availability of the new laboratory and imaging techniques, complete investigations should result in fewer unexplained strokes and more children who can benefit from appropriate, specific treatments designed to prevent stroke recurrence.

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Neuro*Images*

Figure. Chinook arch over Calgary.

Chinook arch over Calgary

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This phenomenon occurs when the warm dry chinook wind blows down from the Rocky Mountains, which can be seen in the background. Downtown Calgary is captured inside the chinook arch and the Calgary International Airport is in the foreground of the picture. The sky is clear over the mountains and the arch is formed by the edge of the cloud formation over the prairies. Chinook winds are a trigger for migraines.

See also pages 280 and 302

