Experimental Intracerebral Hemorrhage in the Mouse
Histological, Behavioral, and Hemodynamic Characterization of a Double-Injection Model

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Background and Purpose—A major limitation of intracerebral hemorrhage (ICH) research is the lack of reproducible animal models. The present study was conducted to validate in the mouse the double-injection method of ICH initially developed in the rat. We investigated the effect of intrastriatal injection of blood or cerebrospinal fluid (CSF) on cerebral blood flow (CBF), neurological score, hematoma volume, and brain swelling.

Methods—Male C57BL/6 mice were anesthetized with halothane/nitrous oxide delivered by face mask. Rectal and cranial temperatures were regulated at 37°C to 37.5°C. Mice were placed in a stereotactic frame, and a 30-gauge stainless steel cannula was introduced through a burr hole into the left striatum. Each mouse received a 5-μL injection of either whole blood or CSF (over 3 minutes), followed 7 minutes later by 10 μL injected over 5 minutes. The injection cannula was slowly withdrawn 10 minutes after the second injection. Control mice had only cannula insertion. CBF was studied by laser Doppler perfusion imaging. Neurological status was evaluated on days 1 and 2. After 2 days, hematoma volume and brain swelling were calculated.

Results—Physiological values were stable. Mice with ICH but not those with CSF or cannula alone had a marked, persistent neurological deficit and a highly reproducible hematoma, whose mean ± SEM volume was 2.0 ± 0.2 mm³ compared with a lesion size of 0.2 ± 0.1 mm³ in mice with CSF. Residual swelling of the ipsilateral hemisphere at 48 hours was 5.7% in the hematoma and 1.5% in the CSF groups. Relative CBF in the neocortex ipsilateral to the injection site declined by ≈45% to 60% during the first 20 minutes after cannula insertion/injection in all groups but began to renormalize at ≈25 to 30 minutes in the CSF and cannula-only groups; in the hematoma group, cortical hypoperfusion of ≈35% to 50% persisted during the 90-minute measurement period.

Conclusions—The present ICH model in mice produces a consistent neurological deficit, hypoperfusion, hematoma volume, and brain swelling. This model closely mimics human hypertensive basal ganglionic ICH and should be useful for the evaluation of pharmaceutical therapies. Laser Doppler perfusion imaging is a useful new technique to quantify relative CBF changes and can be used for studies of dynamic changes of CBF in this in vivo model of ICH in mice. (Stroke. 2003;34:2221-2227.)

Key Words: animal models ■ brain edema ■ intracerebral hemorrhage ■ stroke, experimental ■ mice

Intracerebral hemorrhage (ICH) is a devastating clinical condition, accounting for 15% of all stroke hospitalizations. Currently, there is no medical therapy available for these patients except neurosurgical evacuation of the hematoma. Patients who survive ICH are usually severely disabled; only 10% are capable of living independently after 30 days and only 20% after 6 months. The study of ICH in the mouse has attracted increasing attention, particularly because the availability of genetically modified (transgenic and knockout) mouse strains provides a unique opportunity to evaluate the pathophysiology and therapy of ICH.

Several animal models of ICH have been developed in mice, rat, rabbit, cat, and primates (reviewed elsewhere). A widely used method that produces ICH by injection of bacterial collagenase into the basal ganglia was first introduced by Rosenberg and colleagues in the rat and was subsequently studied in the mouse. This enzyme digests the collagen present in the basal lamina of blood vessels and causes bleeding into the surrounding brain tissue. Although the collagenase method is a simple means of producing hemorrhage and is reproducible, Del Bigio et al demonstrated that bacterial collagenase causes a significant inflammatory reaction and likely differs from the mechanism that produces ICH in humans.

A second model uses the infusion of autologous blood into the brain parenchyma of rats. This model was designed to...
mimic the natural events that occur with spontaneous ICH in humans; however, it produces hematomas of varying size because of ventricular rupture and the backflow of infused blood along the needle track, which leads to intraventricular and/or subarachnoid leakage of blood.\textsuperscript{7} Recently, a double-injection ICH model in the rat has been developed in which a small amount of blood is infused into the striatum at a slow rate to allow blood clotting along the needle track; the remaining blood is then infused to generate the hematoma.\textsuperscript{8,9} This method creates a reproducible hematoma volume suitable for study of the pathophysiology and treatment of ICH.\textsuperscript{9,10}

The present study was conducted to validate a modified double-injection method in the mouse and to assess cerebral blood flow (CBF), neurological score, hematoma volume, and brain swelling.

**Materials and Methods**

**Animal Preparation**

Studies were carried out on male C57BL/6 mice weighing 25 to 30 g obtained from Charles River Laboratories, Inc (Wilmington, Mass). Animal protocols for these studies were approved by the University of Miami Animal Care and Use Committee. The animals were allowed free access to water and food before surgery. Anesthesia was induced by 3% and maintained with 1% halothane in a mixture of 70% nitrous oxide and 30% oxygen delivered by face mask. Temperature probes were inserted into the rectum and the left temporalis muscle, and separate warming lamps were used to maintain rectal (CMA/150 Temperature Controller, CMA/Microdialysis AB) and temporalis muscle (Thermocouple Probe, Omega Engineering) temperature at 36.0°C to 37.5°C. In addition, we allowed mice to recover from surgery in a temperature-controlled incubator and maintained normothermia for 48 hours. Rectal temperature and body weight were measured daily for a 48-hour period.

**Measurement of Physiological Variables**

Because the blood volume required for analytic assays was great enough to cause hypovolemia, a separate series was performed to define the physiological state of mice subjected to ICH. In 3 groups of mice subjected to blood or cerebrospinal fluid (CSF) injection, or needle insertion (n=4 each), the right femoral artery was catheterized into a 1-cm\(^3\) syringe, which was flushed with heparin before blood withdrawal. The injection cannula was slowly withdrawn 10 minutes after the second injection; the wound was sutured; and the animal was placed in an incubator with free access to food and water. In addition, the weight and rectal temperature of each mouse were recorded daily for 2 days. Control mice (n=6) had insertion of only the cannula.

**Model of ICH**

ICH was produced by the double-injection method described for rats.\textsuperscript{8,9} The mouse was placed in a stereotactic frame (David Kopf Instruments). A 30-gauge stainless steel cannula was introduced through a burr hole into the left striatum (2 mm lateral to midline, 1 mm anterior to bregma, depth 4 mm below the surface of the skull). Each mouse received a 5-\(\mu\)L injection of either whole blood (n=15) or CSF (n=6) over 3 minutes, followed 7 minutes later by 10 \(\mu\)L injected over 5 minutes with a microinfusion pump (KDS-100, KDa Scientific). Blood was taken from the heart of a donor mouse with a 1-cm\(^3\) syringe, which was flushed with heparin before blood withdrawal. The injection cannula was slowly withdrawn 10 minutes after the second injection; the wound was sutured; and the animal was placed in an incubator with free access to food and water. In addition, the weight and rectal temperature of each mouse were recorded daily for 2 days. Control mice (n=6) had insertion of only the cannula.

**Laser Doppler Perfusion Imaging**

Cortical perfusion was studied bitemporally through the intact skull with laser Doppler perfusion imaging (LDPI; Moor Instruments, Inc). A midline skin incision \(\approx 2\) cm long was made parallel to the sagittal suture. A computer-controlled optical scanner generated a low-power He-Ne laser beam over the exposed skull. The scanner head was positioned parallel to the skull at a distance of 26 cm. The scanning procedure took 1 minute for measurements covering an area of 2.6\(\times\)2.2 cm (60\(\times\)50 pixels). After baseline images were collected, ICH was produced by injection of blood or CSF as described above. Control mice underwent only cannula insertion.

Two protocols were used in the blood-injected mice. In an initial group (n=5), CBF was measured for 30 minutes after ICH, and a total of 8 images (3 baseline, 5 after ICH) were obtained from each mouse at 5-minute intervals. In a second, larger series (n=7), CBF was measured for 90 minutes after ICH, and a total of 15 images (3 baseline, 10 after ICH) were obtained from each mouse at 5-minute intervals. CSF-injected (n=5) and cannula-only (n=5) groups were also studied for CBF. Five animals (3 from blood, 1 from CSF, 1 from needle insertion group) studied for behavior and histopathology had technically unsatisfactory CBF computer data files and were excluded from CBF analysis.

The analysis of sequential LDPI perfusion images took into account the fact that the LDPI device relative to the mouse head might have to be moved in the course of an experiment; for example, we needed to remove and replace the mirror of the LDPI device to inject blood or CSF. To obtain reliable CBF data from the same location but at different time points, we used an automated registration method developed by our group to align all LDPI images into a uniform geometric coordinate system.\textsuperscript{11} This method is based on an adaptive correlation approach and has been implemented and included in our image-analysis software. In the present experiment, CBF data were acquired by rectangular computer graphic sampling tools simultaneously applied to the entire set of sequential images of a given animal. In this fashion, CBF measurements retained the same sampling size and location, ensuring comparability of CBF data and reliability of the ensuing statistical analysis.

All images were stored in computer memory for subsequent analysis. For each animal, 4 standardized rectangular regions of interest were defined and applied to each image of the series. In each animal, relative perfusion values for each image were then determined as the average of all pixel values within the region of interest divided by the mean of the 3 baseline measurements for that region.

**Behavioral Testing**

A standardized battery of behavioral tests was used to quantify sensorimotor neurological function at 1 or 2, 24, and 48 hour after ICH. The battery consisted of 2 tests that have been used previously to evaluate various aspects of neurologic function: (1) the postural reflex test, which examines upper-body posture while the animal is suspended by the tail,\textsuperscript{12} and (2) the forelimb placing test, which examines sensorimotor integration in forelimb placing responses to visual, tactile, and proprioceptive stimuli.\textsuperscript{13} Neurological function was graded on a scale of 0 to 12 (normal score=0, maximal score=12) as previously described.\textsuperscript{14} Tests were conducted by an observer blinded to the treatment group.

**Histopathology**

Animals were allowed to survive for 2 days. All brains were then perfusion fixed as previously described\textsuperscript{14} with a mixture of 40% formaldehyde, glacial acetic acid, and methanol (1:1:8 by volume), and brain blocks were embedded in paraffin. Sections (10 \(\mu\)m thick) were cut in the coronal plane and stained with hematoxylin and eosin. The following areas were identified on each section: total ipsilateral and contralateral hemisphere areas, area of hematoma, and total affected area (total lesion). To quantify hematoma volume and to depict hematoma frequency distribution, histological sections were digitized at 8 standardized coronal levels (MCID Image-Analysis System, Imaging Research Corp), from which data were exported to a UNIX-based workstation for further processing. An
investigator blinded to the experimental groups outlined the zones of hematoma (which were defined by the presence of blood and microphages) and the left and right hemisphere contours at each level. Software that we developed was then used to quantify hematoma size and brain swelling.

**Statistical Analysis**

Hematoma volumes, brain swelling data, and physiological variables were analyzed with Student’s t tests corrected for multiple comparisons. Total neurological score was compared by the Kruskal-Wallis test. Laser Doppler perfusion data were analyzed by repeated-measures analysis of variance (ANOVA) with posthoc Bonferroni comparisons. Values of P<0.05 were regarded as significant. Values are presented as mean±SEM.

**Results**

Rectal and cranial (temporalis muscle) temperatures, blood gases, and mean arterial blood pressure were similar and showed no significant differences among groups (the Table). Animals began to exhibit neurological signs of an ICH within 60 minutes; mice with ICH (but not those with CSF injection or cannula insertion alone) had marked, persistent contralateral forelimb placing deficits throughout the 2-day observation period after ICH (Figure 1). Histological examination of the brain after 48-hour survival revealed the presence of a localized hematoma in all animals with blood infusion (Figure 2). The measured hematoma volume in the blood-injection group was highly reproducible (Figure 3A). In contrast, the CSF and cannula groups showed only a small, nonhemorrhagic lesion (Figures 2 and 3A). Figure 3B plots lesion areas at 8 representative forebrain levels. Residual swelling of the ipsilateral hemisphere at 48 hours was 5.7% in hematoma mice and 1.5% in the CSF group.

**Physiological Values for Mice Following ICH**

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>CSF</th>
<th>Needle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before ICH (10 min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial temperature, °C</td>
<td>36.4±0.09</td>
<td>36.7±0.12</td>
<td>36.0±0.10</td>
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<tr>
<td>Rectal temperature, °C</td>
<td>37.0±0.04</td>
<td>37.0±0.03</td>
<td>36.9±0.07</td>
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<tr>
<td>pH</td>
<td>7.28±0.05</td>
<td>7.33±0.02</td>
<td>7.32±0.04</td>
</tr>
<tr>
<td>pO2, mm Hg</td>
<td>130±10</td>
<td>127±13</td>
<td>107±6</td>
</tr>
<tr>
<td>pCO2, mm Hg</td>
<td>44.4±4.6</td>
<td>50.0±0.1</td>
<td>46.7±3.3</td>
</tr>
<tr>
<td>MABP, mm Hg</td>
<td>68±4</td>
<td>82±5</td>
<td>76±9</td>
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<tr>
<td>Respiration rate, per min</td>
<td>145±4</td>
<td>148±4</td>
<td>153±4</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>28.7±0.9</td>
<td>28.9±0.8</td>
<td>24.9±1.4</td>
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<tr>
<td>After ICH (15 min)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cranial temperature, °C</td>
<td>36.5±0.08</td>
<td>36.7±0.09</td>
<td>36.8±0.24</td>
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<td>Rectal temperature, °C</td>
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<td>37.0±0.02</td>
<td>37.0±0.03</td>
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<tr>
<td>pH</td>
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<td>7.34±0.04</td>
<td>7.29±0.04</td>
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<tr>
<td>pO2, mm Hg</td>
<td>150±37</td>
<td>109±9</td>
<td>84±12</td>
</tr>
<tr>
<td>pCO2, mm Hg</td>
<td>49±5</td>
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<tr>
<td>MABP, mm Hg</td>
<td>72±8</td>
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<tr>
<td>Respiration rate, per min</td>
<td>142±13</td>
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<td>146±2</td>
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<tr>
<td>After ICH (35 min)</td>
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<td>Cranial temperature, °C</td>
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<td>36.5±0.13</td>
<td>36.9±0.25</td>
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<td>Rectal temperature, °C</td>
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<td>pH</td>
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<td>7.29±0.01</td>
<td>7.29±0.04</td>
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<tr>
<td>pO2, mm Hg</td>
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<td>130±21</td>
<td>84±8</td>
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<td>pCO2, mm Hg</td>
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<td>53±1</td>
<td>50±3</td>
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<td>MABP, mm Hg</td>
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<td>80±10</td>
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<td>Respiration rate, per min</td>
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<td>148±3</td>
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<tr>
<td>After ICH (24 h)</td>
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<td></td>
</tr>
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<td>Rectal temperature, °C</td>
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<td>36.3±0.33</td>
<td>36.5±0.75</td>
</tr>
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<td>After ICH (48 h)</td>
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<td>36.5±0.48</td>
<td>36.9±0.76</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>26.3±1.01</td>
<td>22.9±1.33</td>
<td>22.9±1.33</td>
</tr>
</tbody>
</table>

ICH indicates intracerebral hemorrhage; MABP, mean arterial blood pressure.

Value are mean±SEM.
insertion/injection in all groups but began to renormalize by ≈25 to 30 minutes in the CSF and cannula-only groups; in the hematoma group, cortical hypoperfusion (by ≈35% to 40% in left 1 area and by ≈45% to 50% in left 2 area; Figures 4 and 5) persisted during the 90-minute measurement period. Relative CBF values in the cannula and needle-only control groups did not differ significantly from each another at any time point.

Discussion

Model of ICH

We have validated a mouse adaptation of the double-injection model of ICH, previously described in rats. We demonstrate that our modification produces a localized clot in the brain parenchyma in the striatum after blood injection. The presence of a 15-μL blood clot produced consistent histological changes with marked neurological disability. As opposed to the rapid injection of blood used in previous models, this model used a slow infusion of fresh donor blood into the brain parenchyma. This modified technique is consistent with recent clinical evidence indicating a gradual evolution of mass effect, initially over the first 2 days as a result of hematoma enlargement and later during the second and third weeks associated with an increase in brain edema. We think that the slow infusion of blood limits its extravasation into the subarachnoid and ventricular spaces and more closely mimics the natural process. Furthermore, it also avoids undesired nonphysiological pressure injury to adjacent tissue. In the present study, only 2 mice developed intraventricular hemorrhage and were excluded from the analysis.

CBF and Brain Swelling

The pathophysiology of ICH is complex. Hemorrhage into the brain initially results in a mass effect with compression of the adjacent microvasculature by the hematoma. This is followed by development of brain edema and possibly damage caused by raised intracranial pressure with local reductions in CBF.

Measurements of local CBF in rats after ICH have shown an immediate reduction of CBF to ischemic levels (<25 mL · 100 g⁻¹ · min⁻¹) both in areas surrounding the clot and in more distant regions after injection of 25 to 100 μL blood. Blood flow in the cerebral hemisphere was reduced to 50% of control at 1 hour after ICH but returned to baseline by 4 hours, where it remains for the next 24 hours. Other studies in rats also showed that CBF is reduced in the tissue around an intracranial mass and may contribute to delayed brain edema in this region. In contrast, a recent study in humans with acute ICH, which used PET to assess both CBF and cerebral oxygen use and oxygen extraction fraction (OEF), found that cerebral oxygen use was depressed to a greater
extent than CBF in the periclot region, resulting in reduced rather than elevated oxygen extraction fraction, implying that the periclot hypoperfusion was insufficient to induce true tissue ischemia.19

Previous studies in rats suggest that CBF changes after ICH vary in different regions of the brain; thus, we studied regional CBF changes in different zones based on their topographic locations with respect to the hematoma (Figures 4 and 5). No previous studies have reported CBF levels and dynamic blood flow changes in mice after ICH. Our results in mice show an early decrease in CBF to ~40% to 55% of control values during the first ~20 minutes after blood

Figure 4. Representative color-coded LDPI through mouse skull in blood- and CSF-injected mice. Color bar shows arbitrary linear perfusion units. Horizontal black bar denotes the longitudinal midline (anterior to the left). Central rectangle denotes the bregma. Small ellipses indicate site of cannula penetration for blood or CSF injection. Four rectangular regions of interest were analyzed ipsilateral (left 1, left 2) and contralateral (right 1, right 2) to affected hemisphere. Blood injection is associated with decreased ipsilateral cortical perfusion at 10 and 60 minutes after ICH, CSF caused temporary reduction in ipsilateral cortical perfusion at 10 minutes, which tended to renormalize by 60 minutes.

Figure 5. Relative cortical perfusion measured by scanning LDPI in mice with ICH and pooled controls (CSF injection or cannula insertion alone). Values were computed in each animal as percentage decrements compared with average of 3 preinsult baseline measurements and are expressed as mean±SEM. For ICH mice, n=12 for the first 15 minutes, and n=7 for the subsequent time points. For the control group, n=10. The 4 regions of interest used for analysis are shown in Figure 4.
injection and persistent reductions to ≈50% to 65% of control levels for an additional 1 hour. In contrast, CSF injection or cannula insertion led to less pronounced (except for the first 10 minutes) and more transient CBF reductions, which began to renormalize after ≈25 to 30 minutes (Figure 5). Although CBF tended to decrease slightly in the contralateral hemisphere, these changes were not significant (Figure 5).

Diffuse declines in CBF have also been shown in patients with ICH. A global effect of the hematoma on CBF, however, does not explain the injury produced by most hematomas. An average-sized hematoma in patients has little effect on intracranial pressure or CBF, because that volume is well within the volume-buffering capacity of the intracranial space.20 We think that the slow infusion of blood in our model (as opposed to previous models, in which a single bolus of blood was injected over a much shorter period) may have allowed better buffering of the intracranial pressure and regional CBF.

There is evidence that intracerebral blood causes delayed damage through a variety of other mechanisms, including release of toxic substances such as thrombin and hemoglobin from the blood clot, inflammatory cell infiltration, and microglia reactions (for general discussions, see elsewhere1,21-23).

An important component of the present study was the application of LDPI to measure sequential perfusion changes after ICH. LDPI is a new technique for repeatedly assessing perfusion changes over a wide brain by scanning a low-power laser beam across the brain. Moving blood in the microvasculature causes a Doppler shift, which is processed to build up a color-coded image of blood flow. Thus, LDPI can depict both dynamic changes and regional differences.24 In contrast, conventional laser Doppler flowmetry is a real-time measure but is restricted to a single point on the cortical surface. In the mouse, the technique can be applied through the intact skull, so only scalp reflection is needed.

Brain edema is an important clinical complication of ICH.24 Previous studies in rats with ICH indicate that brain edema increases progressively in the first 24 hours, accompanied by the expected shifts in sodium and potassium content.7 Brain water content remains elevated for several days and then begins to resolve after 4 to 5 days.7 Although we did not measure water content, our volumetric measurement of left and right hemispheres also showed residual swelling of the ipsilateral hemisphere at 48 hours in blood-injected mice, whereas almost no swelling was present in the CSF and cannula-only groups.

Importance of Histopathological Evaluation
The most frequent sites of primary spontaneously ICH in human are the putamen (50%), thalamus (15%), pons (10% to 15%), and cerebellum (10%).25 In the present study, we used injection of blood into the striatum to create the situation that may be relevant to clinical ICH. We observed a localized striatal hematoma in all mice with blood infusion. In contrast, the CSF-injected group showed only a small, nonhemorrhagic lesion. We quantified histopathology at 8 coronal levels using perfusion-fixed, paraffin-embedded material. Previous studies in the mouse have, in general, relied on the use of the triphenyltetrazolium staining method at relatively few coronal levels. Although the triphenyltetrazolium method is quicker and hence easier, we believe that the more extensive analysis of lesion topography possible with paraffin-embedding and close sectioning is advantageous. A major advantage is that such material is readily amenable to detailed analysis by sophisticated image-averaging methods.14,26

Importance of Neurological Evaluation
Observation of neurological deficits is important not only in clinical stroke patients but also in animal models of ICH. A battery of tests for assessing acute changes in sensorimotor function has been developed for rat and mouse models of unilateral brain injury such as cerebral ischemia12-14 and ICH.3,27 Two sensorimotor tests appear to be particularly sensitive in detecting deficits after unilateral brain injury in the mouse: the postural reflex test and the forelimb placing test.14,28 In this experiment, we observed marked, persistent contralateral forelimb placing deficits after blood injection but not after CSF injection or cannula insertion alone.

Importance of Temperature
It is now well recognized that even small decreases in brain temperature protect the brain from ischemic injury (for review, see the work by Busto and Ginsberg29). Connolly et al30 demonstrated that mice after middle cerebral artery occlusion fail to regulate their temperatures, becoming severely hypothermic during the postoperative period, and that these temperature changes may have a profound effect on histopathological outcome after focal cerebral ischemia. There was no significant difference between the groups in temperature over the 48-hour time period.

Conclusions
The present ICH model in mice produces a consistent neurological deficit, hematoma volume, brain swelling, and cortical hypoperfusion. This model closely mimics human hypertensive basal ganglionic ICH and should be useful for the evaluation of pharmaceutical therapies. LDPI is a useful new technique to quantify relative CBF changes and can be used for studies of dynamic changes of CBF in this in vivo model of ICH in mice.

Acknowledgments
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References


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