Intracerebral hemorrhage (ICH) is associated with poor functional outcome and mortality rates of ≈40%. The precise pathogenesis of perihematoma edema and its relationship to secondary brain injury is uncertain. It is becoming increasingly clear that perihematoma edema is not cytotoxic or indicative of an ischemic process. Vasogenic edema, or increased fluid movement from the intravascular to extracellular space, has been postulated as an alternative mechanism of edema formation. Fluid shifts from the vascular compartment can occur with or without blood–brain barrier (BBB) compromise. The extent of BBB compromise in ICH is unknown.

In the recently completed Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH ADAPT), we used computed tomographic perfusion (CTP) to measure cerebral blood flow after acute blood pressure (BP) reduction in ICH patients. The rate of iodinated contrast extravasation during CTP acquisition can be used to calculate permeability-surface area product (PS), an estimate of BBB permeability. Using ICH ADAPT data, we tested the hypotheses that (1) PS is increased in the perihematoma region and predicts perihematoma edema growth, (2) PS elevation is predictive of perihematoma edema growth, and (3) PS changes are associated with acute BP reduction.
Methods

Patients
All patients were enrolled in ICH ADAPT, a prospective, randomized clinical trial evaluating the effect of BP reduction on cerebral blood flow (clinicaltrials.gov NCT00963976). The ICH ADAPT protocol has been described previously. Patients with ICH aged ≥18 years were randomized within 24 hours of onset to a systolic BP target (SBP) of <150 or <180 mm Hg and underwent CTP imaging 2 hours later. Randomization was stratified by time from onset (0–6 and 6–24 hours). Informed consent was obtained from each patient or an authorized representative. Human ethics committees at each site approved the study protocol.

BP Protocol
A protocol based on intravenous labetalol, hydralazine, and enalapril was used to achieve BP targets. Automated cuffs were used to record BP. In the case of missing BP time points, the last observation was carried forward, or the average of existing data points was taken. Weighted average BPs were calculated as the area under the curve describing pressures >2 hours and 24 hours, as previously described.

Image Acquisition
Patients underwent noncontrast CT scans at baseline, 2±1 hours, and 24±3 hours after randomization. The noncontrast CT scan protocol consisted of 18 to 20 5-mm slices through the whole brain with a 512×512 matrix (120 kVp, 300 mA per slice). CTP imaging was performed at 2 hours, within a 38×80-mm section framing the noncontrast CT slice where hematoma diameter was largest. Iodinated contrast injection (40–50 mL) was delivered into an antecubital vein. CTP images were acquired every 1 s for 50 s, and CTP slab thickness and acquisition protocol varied with scanner capability.

Image Analysis
Postprocessing of raw CTP source images was completed centrally on a Siemens Syngo MMWP VE36A workstation. CTP maps were derived from the tissue time–density curve and contrast bolus delay and dispersion were corrected for using a singular value deconvolution algorithm. PS maps were derived using a modified first-pass 2-compartment Patlak model.

Region of interest (ROI) analyses were completed using the Analyze 11.0 software package. ROIs were drawn using planimetric techniques on CTP base images and then transferred to the corresponding PS maps. ROIs included the hematoma, a 1-cm region surrounding the hematoma, contralateral mirror regions, and both hemispheres (Figure 1A). Relative PS (rPS) was calculated as the ratio of contralateral to ipsilateral PS in each ROI.

Hematoma, total ICH (hematoma+intraventricular hemorrhage [IVH]), and edema volumes were measured independently by 2 investigators (R.M. and B.G.) on noncontrast CTs at each time point. Hematoma volumes were defined using semiautomated Hounsfield Unit thresholding. Perihematoma edema volume and relative edema (edema volume/hematoma volume, as previously described) were measured using a threshold of 5 to 23 Hounsfield Unit, which has been demonstrated to be the most reliable CT Hounsfield Unit threshold for edema.

Statistical Analysis
Statistical analysis was performed using SPSS 21.0 (SPSS Inc, Chicago, IL). Comparison of baseline mean characteristics between the 2 treatment groups was made using independent t tests, Mann–Whitney tests, or Pearson χ² tests. BP between treatment groups was considered statistically different when the 95% confidence intervals of the mean values for each time point did not overlap. The relationships between edema, PS, and BP parameters were assessed using linear regression. Paired t tests were used to assess mean PS differences between hemispheres.

Results
Patient Characteristics
Seventy-five patients were randomized in ICH ADAPT. The present analysis was limited to 1 follow-up CT scan for assessment of edema volume growth. A total of 53 patients met these inclusion criteria; 22 patients were excluded because of lack of PS maps (n=20), death (n=1), or surgery (n=1) before the 24-hour follow-up scan. Median (interquartile range) time from symptom onset to CTP was 10.8 hours (14.4).

At baseline, median (interquartile range) hematoma volume for all patients was 15.6 (19.7) mL and edema volume was 1.65 (3.4) mL. Median relative edema in patients randomized within 6 hours of onset (n=23; 0.1 [0.1]) was similar to that in patients randomized within 6 to 24 hours (n=30; 0.2 [0.2]; P=0.123).

The <150 mm Hg (n=26) and the <180 mm Hg (n=27) treatment groups were balanced with respect to clinical characteristics, baseline volumes, and time to randomization (Table 1).

BBB Permeability
Discrete regions of focally elevated BBB permeability were found in the hematoma, perihematoma, and ipsilateral hemisphere of most patients (Figure 2). One patient had a spot sign that corresponded with increased PS (Figure 1B). Mean PS in the hematoma (6.6±2.8 mL/100 mL per minute) was higher than that in contralateral mirror region (3.6±1.7 mL/100 mL per minute; P<0.0001). Mean perihematoma PS (5.1±2.4 mL/100 mL per minute) was also elevated relative to contralateral regions (3.6±1.6 mL/100 mL per minute; P<0.001). Mean PS in the ipsilateral hemisphere (4.2±2.1 mL/100 mL per minute) was higher than that in the contralateral hemisphere (3.7±1.6 mL/100 mL per minute; P=0.002; Figure 2).

Linear regression revealed no relationship between baseline hematoma volume and either hematoma PS (β=0.149 [−0.05
Relative perihematoma PS was not correlated with relative edema volume at baseline (β = −0.025 [−0.21 to 0.17]; P = 0.858), 2 hours (β = −0.078 [−0.21 to 0.12]; P = 0.583) or 24 hours after symptom onset (β = −0.257 [−0.34 to 0.02]; P = 0.078). Relative perihematoma PS did not predict relative edema growth from 0 to 24 hours (β = −0.192 [−0.06 to 0.01]; P = 0.190; Figure 3A). Multivariate regression using BP treatment group and IVH as independent variables did not affect the relationship between baseline perihematoma volume and perihematoma rPS (β = −0.093 [−0.16 to 0.08]; P = 0.517).

BP Changes
Mean SBP 2 hours after randomization in the <150 mm Hg group (139.2 ± 22.1 mm Hg) was significantly lower than that in the <180 mm Hg group (159.7 ± 12.3 mm Hg; P < 0.0001). Mean weighted SBP was different between treatment groups during the first 2 hours (147 ± 13 mm Hg in the <150 target group vs. 161 ± 14 mm Hg in the <180 target group; P = 0.001) and first 24 hours after randomization (141 ± 9 versus 152 ± 13 mm Hg; P < 0.0001; Figure 4).

Relationship Between BP and Permeability
Mean PS in all regions was similar between the 2 BP treatment groups (Table 2). Weighted average SBP at 2 hours did not predict mean rPS in the hematoma (β = 0.100 [−0.05 to 0.10]; P = 0.477) or perihematoma region (β = 0.101 [−0.02 to 0.04]; P = 0.472). There was no relationship between change in SBP (0–2 hours) and hematoma rPS (β = −0.091 [−0.05 to 0.03]; P = 0.518; Figure 3B) or perihematoma rPS (β = −0.205 [−0.02 to 0.004]; P = 0.141; Figure 3C). Change in SBP was not related to permeability in any other ROIs.

Baseline SBP did not predict relative edema volume at baseline (β = 0.001 [−0.01 to 0.01]; P = 0.996) or edema growth > 24 hours (β = −0.085 [−0.003 to 0.002]; P = 0.566). The change in SBP was also not predictive of edema growth (β = −0.092 [−0.002 to 0.001]; P = 0.536).

Perihematoma Edema and Hematoma Volumes
Median hematoma volume was stable between the baseline and 24 hours scans in both treatment groups (Table 2). Hematoma expansion (> 6 mL or > 1/3 of baseline) was seen in 7 patients in each of the <150 and <180 mm Hg groups (P = 1.00). The absolute increase in edema volume from 0 to 24 hours was 3.0 ± 6.9 mL and was similar in both groups (Table 2). Acute hematoma volume predicted absolute perihematoma edema volume at baseline (β = 0.642 [0.35–0.70]; P < 0.0001). The change in

Table 1. Baseline Characteristics Between Blood Pressure Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>&lt;150 mm Hg Target (n=26)</th>
<th>&lt;180 mm Hg Target (n=27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>71.0±12.6</td>
<td>70.2±10.2</td>
<td>0.77</td>
</tr>
<tr>
<td>Men</td>
<td>18 (69%)</td>
<td>20 (74%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Symptom onset to randomization, h, median (IQR)</td>
<td>9.4 (15.0)</td>
<td>9.33 (13.5)</td>
<td>0.86</td>
</tr>
<tr>
<td>Symptom onset to acute NCCT, h</td>
<td>2.72 (3.68)</td>
<td>2.28 (1.77)</td>
<td>0.79</td>
</tr>
<tr>
<td>Randomized &lt;6 h</td>
<td>12 (46%)</td>
<td>11 (40%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (69%)</td>
<td>19 (70%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>3 (11%)</td>
<td>0 (0%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>5 (19%)</td>
<td>1 (4%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Medication history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombotics</td>
<td>3 (11%)</td>
<td>4 (15%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Antihypertensive use</td>
<td>12 (46%)</td>
<td>10 (37%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>180±20</td>
<td>181±25</td>
<td>0.89</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>92±18</td>
<td>94±25</td>
<td>0.77</td>
</tr>
<tr>
<td>Heart rate, bpm*</td>
<td>72±11</td>
<td>80±15</td>
<td>0.77</td>
</tr>
<tr>
<td>NIHSS score, median (IQR)</td>
<td>10 (12)</td>
<td>9 (10)</td>
<td>0.48</td>
</tr>
<tr>
<td>GCS, median (IQR)</td>
<td>15 (3)</td>
<td>15 (1)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hematoma volume, mL</td>
<td>15.0 (21.1)</td>
<td>17.1 (26.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>Intraventricular volume, mL</td>
<td>0.0 (0.6)</td>
<td>0.0 (3.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>4 (15%)</td>
<td>11 (41%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Total ICH volume, mL</td>
<td>15.1 (22.4)</td>
<td>19.2 (32.8)</td>
<td>0.46</td>
</tr>
<tr>
<td>Relative edema volume (5–23 HU), mL</td>
<td>0.11 (0.16)</td>
<td>0.13 (0.21)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; bpm, beats per minute; GCS, Glasgow Coma Scale; HU, Hounsfield Units; ICH, intracerebral hemorrhage; IQR, interquartile range; NCCT, noncontrast computed tomography; and NIHSS, National Institutes of Health Stroke Scale.

* <150 mm Hg group (n=25).
absolute edema volume >24 hours was also predicted by acute hematoma volume ($\beta=0.303$ [0.01–0.42]; $P=0.036$).

**Discussion**

We found that BBB permeability is focally increased in the hematoma, perihematoma, and ipsilateral hemisphere in acute ICH patients. The absolute increase in each region was small and did not predict acute perihematoma edema volume. These results indicate that BBB compromise is unlikely to be a major factor in perihematoma edema formation. Acute BP reduction did not affect either BBB permeability or edema growth.

**BBB Permeability**

A modest focal elevation of mean BBB permeability was observed in the hematoma. The highest PS values were observed in a single patient with a visible spot sign$^{15}$ on CTP source images (Figure 1B). This confirms that elevated PS represents contrast extravasation.

![Figure 3](image-url) Scatter plots with linear regression coefficients and 95% confidence intervals. **A**, Relative edema growth >24 hours was unrelated to blood–brain barrier permeability-surface area product (PS). Edema volumes were natural log-transformed. Change in systolic blood pressure (SBP) did not predict relative hematoma (B) or PS (C).

![Figure 4](image-url) Average systolic blood pressure (SBP) changes >24 hours in the treatment groups. Mean SBP differences were considered statistically significant (*) if the 95% confidence intervals (not shown for clarity) did not overlap.
Table 2. Effects of Blood Pressure Treatment on Blood–Brain Barrier Permeability, Hematoma and Edema Growth, and Clinical Outcome

<table>
<thead>
<tr>
<th>PS measures, mL/100 mL per minute (mean±SD)</th>
<th>&lt;150 mmHg Target (n=26)</th>
<th>&lt;180 mmHg Target (n=27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma PS</td>
<td>6.5±2.6</td>
<td>6.7±3.0</td>
<td>0.81</td>
</tr>
<tr>
<td>Perihematomal PS</td>
<td>4.9±2.4</td>
<td>5.3±2.4</td>
<td>0.51</td>
</tr>
<tr>
<td>Ipsilateral hemispheric PS</td>
<td>4.0±2.0</td>
<td>4.5±2.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Contralateral hemispheric PS</td>
<td>3.4±1.3</td>
<td>3.9±1.8</td>
<td>0.30</td>
</tr>
<tr>
<td>Hematoma rPS</td>
<td>4.5±2.3</td>
<td>4.8±5.3</td>
<td>0.75</td>
</tr>
<tr>
<td>Perihematoma rPS</td>
<td>3.4±1.5</td>
<td>3.0±1.4</td>
<td>0.36</td>
</tr>
<tr>
<td>Hemispheric rPS</td>
<td>2.3±0.6</td>
<td>2.3±0.7</td>
<td>0.93</td>
</tr>
</tbody>
</table>

5–23 HU edema measures (mean±SD)

- 2-h relative edema volume, mL*: 0.20±0.17 vs. 0.17±0.11 (P=0.46)
- 24-h relative edema volume, mL: 0.28±0.20 vs. 0.23±0.18 (P=0.39)
- Change in absolute volume (0–24 h), mL (median (IQR)†: 1.5 (2.9) vs. 0.98 (2.0) (P=0.45)
- Change in relative volume (0–24 h), mL‡: 0.13±0.19 vs. 0.06±0.16 (P=0.24)

Hematoma measures, median (IQR)

- 2-h hematoma volume, mL: 14.6 (20.6) vs. 16.9 (27.3) (P=0.97)
- 24-h hematoma volume, mL: 16.2 (28.3) vs. 16.8 (30.0) (P=0.88)
- Hematoma growth from 0 to 24 h, mL: 0.85 (7.6) vs. 0.40 (3.0) (P=0.26)
- Hematoma expansion (>6 mL or >1/3 growth): 7 (28%) vs. 7 (28%) (P=1.00)

Clinical outcomes, median (IQR)

- Change in SBP (0–2 h), mm Hg (mean±SD): -41±31 vs. -22±25 (P=0.014)
- SPB at 2 h, mm Hg (mean±SD): 139±22 vs. 160±12 (<0.0001)
- BP load, % time spent >180 mm Hg: 0.5 (2.1) vs. 4.2 (7.3) (P=0.02)
- BP load, % time spent <150 mm Hg: 76.1 (19.8) vs. 33.3 (53.2) (<0.0001)
- Weighted average SBP at 2 h, mm Hg: 147±13 vs. 161±14 (P=0.001)
- Weighted average SBP at 24 h, mm Hg: 141±9 vs. 152±13 (<0.0001)
- NIHSS score at 2 h: 11.0 (13) vs. 9 (10) (P=0.60)
- NIHSS score at 24 h: 9.0 (13) vs. 8.0 (12) (P=0.83)
- 30-d mortality: 4 (15%) vs. 2 (7%) (P=0.36)
- 90-d Barthel Index: 90 (98) vs. 100 (45) (P=0.58)
- 90-d mRS: 3 (4) vs. 2 (3) (P=0.86)
- 90-d NIHSS: 4 (31) vs. 3 (5) (P=0.79)

In the perihematoma and hemispheric regions, the absolute increase in PS was moderate (Figure 1A). Increased permeability may be secondary to the mechanical effects of the hematoma or the toxic effects of blood breakdown products. In animal models of acute ICH, BBB compromise has been observed in the perihematoma region within 24 hours and 48 hours of onset. In contrast to the uniform and striking PS elevations seen in tumors, we found only modest focal increases in BBB permeability, which were unrelated to edema growth. This is inconsistent with a vasogenic process as the major mechanism underlying edema formation. Minor BBB permeability increases were observed in the perihematoma region in a recent MRI study, based on Ktrans measurements. The authors found a mild association between BBB leakage and edema volume 1 day after onset, although the study included 60% nonspontaneous ICH patients.

PS is a validated technique which has predictive utility in stroke medicine. Elevated PS is a robust predictor of hemorrhagic transformation after ischemic stroke. After ischemia, the endothelium is damaged, resulting in blood extravasation from the vessels. The limited areas of elevated perihematoma permeability in ICH may also result from injured endothelium. Alternatively, it is possible that elevated PS represents a bleeding vessel, rather than BBB compromise per se. In this context, elevated PS may predict hematoma expansion and therefore perihematoma edema expansion. However, we are unable to test this hypothesis, as the majority of our patients were studied after the 24-hour period where hematoma expansion is most common.

Edema Pathogenesis

We have previously demonstrated that perihematoma edema in acute ICH is unrelated to decreases in perihematoma cerebral blood flow. Elevated diffusion rates in the perihematoma region have been demonstrated in previous MRI studies, which do not indicate that this edema is cytotoxic. Thus, perihematoma edema does not seem to be primarily cytotoxic or vasogenic in origin. It has been postulated that edema represents successful hemostasis as serum extrudes from the contracting clot within the first hours and days after ICH. Fluid originating from the hematoma is redistributed as edema, with no net addition of fluid from the vascular compartment. This is consistent with our finding that BBB permeability in the perihematoma region and throughout the brain is largely preserved and not associated with changes in edema volume.

IVH extension seemed to be more common in the <180 mmHg BP group, although the difference was not significant (P=0.07). IVH may theoretically be associated with a decrease in parenchymal blood breakdown products, secondary to a decompressive effect after rupture into the ventricle. This could potentially result in lower edema volumes. This is unlikely, however, given the results of the multivariate regression model in which IVH and BP treatment groups were included as independent variables. The presence of IVH did not affect the relationship, or lack thereof, between baseline edema and perihematoma PS.
BP and Permeability

We hypothesized that increased BP, and correspondingly increased perfusion pressure, would affect the rate of BBB leakage in acute ICH. An association between high BP, BBB permeability, and hemorrhagic transformation has been demonstrated in an ischemic model of rats. A study in a mouse model of induced hypertension found that intra-abdominal tension, which can increase cerebral perfusion pressure, resulted in temporarily increased BBB permeability. We found no relationship between BP and the focal PS increases in any of the studied regions. Although biologically plausible, our results provide no support for the hypothesis that edema growth is attenuated by BP lowering.

BP and Edema Growth

We found no relationship between edema volume and either presenting BP or change in BP. Patients in the <150 and <180 mm Hg groups had similar edema volumes at baseline, 2 hours, or 24 hours (Table 2). Furthermore, BP was not predictive of edema growth from 0 to 24 hours. These data are consistent with the results of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT). In this trial, proportional and absolute edema volume increases >72 hours were not significantly different between <140 and <180 mm Hg treatment groups.

Study Limitations

The relatively small sample size limits the confidence with which we can rule out an interaction between BP reduction and perihematoma edema growth. The results of the PS measurements were highly consistent in all patients, however, making it unlikely that elevated BBB permeability is a major mechanism of edema formation.

The CTP measurement technique used in this study was first-pass with a short acquisition time (50 s). In conditions associated with vasogenic edema, first-pass CTP imaging is capable of demonstrating BBB leakage. First-pass CTP estimates of BBB permeability tend to overestimate, rather than underestimate, contrast leakage rates when compared with 2-phase perfusion imaging.

Conclusions

Limited focal increases in BBB permeability are present within the perihematoma region of acute ICH patients. These increases are insufficient to result in the observed increase in perihematoma edema volume after ICH. We found no effect of BP reduction on either BBB permeability or perihematoma volume growth.

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Disclosures

Dr Butcher holds a Canada Research Chair in Cerebrovascular Disease, a Heart and Stroke Foundation of Alberta (HSFA) Professorship in Stroke Medicine and a New Investigator Award from Alberta Innovates Health Solutions (AIHS). Dr Hill holds a HSFA Professorship in Stroke Medicine. Dr Demchuk holds a HSFA Chair in Stroke Medicine. Dr Coutts holds an AIHS New Investigator award. Dr Kosior has an Alberta Innovates Technology Futures Fellowship. The other authors report no conflicts.

References


Blood–Brain Barrier Compromise Does Not Predict Perihematoma Edema Growth in Intracerebral Hemorrhage

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