Cerebral Perfusion and Blood Pressure Do Not Affect Perihematoma Edema Growth in Acute Intracerebral Hemorrhage

Rebecca McCourt; Bronwen Gould, BSc; Laura Gioia, MD; Mahesh Kate, MBBS, MD; Shelagh B. Cottus, MBChB, MD; Dariush Dowlatshahi, MD, PhD; Negar Asdaghi, MD, MSc; Thomas Jeerakathil, MD, MSc; Michael D. Hill, MD, MSc; Andrew M. Demchuk, MD; Brian Buck, MD; Derek Emery, MD, MSc; Kenneth Butcher, MD, PhD; on behalf of the ICH ADAPT Investigators

Background and Purpose—The pathogenesis of perihematoma edema in intracerebral hemorrhage (ICH) is unknown but has been hypothesized to be ischemic. In the ICH Acutely Decreasing Arterial Pressure Trial (ICH ADAPT), perihematoma cerebral blood flow (CBF) was reduced but was unaffected by blood pressure (BP) reduction. Using ICH ADAPT data, we tested the hypotheses that edema growth is associated with reduced CBF and lower systolic BP.

Methods—Noncontrast computed tomographic scans in patients with ICH were obtained at baseline, 2 hours, and 24 hours after randomization to target systolic BPs of <150 or <180 mmHg. Computed tomography perfusion imaging was performed at 2 hours, and mean relative CBF was calculated in visibly edematous perihematoma tissue. Edema volumes were measured using a Hounsfield unit threshold of 5 to 23 at each time-point.

Results—Patients were randomized at a median (interquartile range) of 7.4 (12.8) hours after onset. Treatment groups (n=34, <150 and n=33, <180 target) were balanced with respect to baseline systolic BP and acute ICH volume. Relative edema growth at 24 hours in the <150 group (0.11±0.19) was similar to that in the <180 group (0.09±0.16 mL; P=0.727). Absolute CBF was lower in the edematous region (35.67±13.1 mL/100 g per minute) when compared with that in the contralateral tissue (43.7±11.7 mL/100 g per minute; P<0.0001). Linear regression indicated that neither systolic BP change (β=–0.022; 95% confidence interval, –0.002 to 0.001) nor perihematoma relative CBF (β=–0.144; 95% confidence interval, –0.647 to 0.167) predicted edema growth.

Conclusions—Lower perihematoma CBF and BP treatment do not exacerbate edema growth. These data do not support a cytotoxic edema pathogenesis.

Key Words: brain ◼ cerebral hemorrhage ◼ edema ◼ hypertension ◼ perfusion imaging

Perihematoma edema becomes visible on computed tomography (CT) within 3 hours of intracerebral hemorrhage (ICH) onset.1 The precise pathogenesis of perihematoma edema is uncertain and controversial. Cerebral blood flow (CBF) is lower in the perihematoma region,2–5 and MRI studies5,6 have demonstrated areas of restricted diffusion that may represent a cytotoxic process. The potential for secondary perihematoma ischemia has contributed to a cautious approach to acute blood pressure (BP) reduction.7,8 There is also evidence that perihematoma edema is at least partly vasogenic or plasma derived.3,4,9 Acute BP reduction may, therefore, reduce perihematoma volume growth, via decreased hydrostatic pressure.

The recently completed ICH Acutely Decreasing Arterial Pressure Trial (ICH ADAPT)10 randomized patients to a systolic BP (SBP) target of <150 or <180 mmHg. The primary ICH ADAPT results indicate that perihematoma CBF is moderately reduced in ICH but remains above ischemic thresholds irrespective of BP reduction. In this secondary ICH ADAPT analysis, we evaluated the relationship between perihematoma CBF reduction and edema growth. We also evaluated, for the first time, perfusion measures in the perihematoma edematous...
tissue. We tested the hypotheses that perihematoma edema growth is associated with (1) lower CBF and (2) decreased SBP.

**Methods**

**Patients**

The ICH ADAPT protocol (clinicaltrials.gov NCT00963976) has been described previously. Briefly, patients with ICH aged ≥18 years presenting within 24 hours of onset were randomized to a target SBP of <150 or <180 mm Hg, followed by CT perfusion (CTP) imaging 2 hours later. Informed consent was obtained from each patient or an authorized representative. Human ethics committees at each site approved the study protocol.

**BP Treatment and Clinical Assessments**

Intravenous antihypertensive agents (labetalol/hydralazine/enalapril) were used to achieve target SBPs within 1 hour of randomization. Automated BP cuffs were used to record BP every 15 minutes during the first hour after randomization, every 30 minutes for 6 hours, and every hour thereafter, from 7 to 24 hours. National Institutes of Health Stroke Scale scores were recorded at baseline, 2 hours, 24 hours, and at 90 days.

Weighted average BPs were calculated as the area under the curve describing pressures >24 hours, as previously described. High and low BP loads (fraction of time spent >180 or <150 mm Hg, respectively) were also calculated, as previously described.13

**Image Acquisition**

Patients underwent noncontrast CT (NCCT) scans at baseline, 2±1 hours, and 24±3 hours after randomization. CTP imaging was performed during the first hour after randomization, every 30 minutes for 6 hours, and every hour thereafter, from 7 to 24 hours. Intravenous antihypertensive agents (labetalol/hydralazine/enalapril) were used to achieve target SBPs within 1 hour of randomization. Automated BP cuffs were used to record BP every 15 minutes during the first hour after randomization, every 30 minutes for 6 hours, and every hour thereafter, from 7 to 24 hours. National Institutes of Health Stroke Scale scores were recorded at baseline, 2 hours, 24 hours, and at 90 days.

Weighted average BPs were calculated as the area under the curve describing pressures >24 hours, as previously described. High and low BP loads (fraction of time spent >180 or <150 mm Hg, respectively) were also calculated, as previously described.13

**Image Analysis**

All images were postprocessed and measured centrally. Raw CTP source images were analyzed on a Mac workstation using the PeriScape analysis package (PeriScape 2.9 CT Stroke Edition; Olea Medical, Marseilles, France). CTP maps were derived from the tissue time–density curve. Corrections for delay in contrast arrival and dispersion of the bolus were made using an arrival time-insensitive single value deconvolution algorithm.14

All hematoma, edema, and perfusion parameter volumes were measured using the Analyze 11.0 software suite (Biomedical Imaging Resource; Mayo Clinic). Mean transit time, cerebral blood volume (CBV), and CBF maps were calculated. Voxels containing blood vessels were removed using an intensity threshold function of CBF >100 mL/100 g per minute or CBV >8 mL/100 g. Regions of interest (ROIs) were drawn on CTP source images, using planimetric techniques. ROIs consisted of a 1-cm region surrounding the hematoma (labeled edematous region). Relative perfusion measures were calculated as the ratio (for relative CBF [rCBF] and relative CBV), or difference (for relative mean transit time), between absolute ipsilateral and contralateral values in each region. Relative perfusion in the edematous region was calculated as perfusion in the edematous area/perfusion in the contralateral 1-cm region.

Hematoma and edema ROI measurements were completed independently by 2 investigators (R.M. and B.G.) on NCCTs at all time-points. Hematoma and total ICH (calculated as hematoma+intraventricular hemorrhage) volumes were measured using semiautomated thresholding techniques. Perihematoma edema volume ROIs (ie, edema volumes) were first drawn manually on NCCTs by the 2 raters independently. A second set of measurements was obtained by applying a threshold of 5 to 23 HU to the manual ROIs.15 Relative edema volume (5–23 HU edema volume/hematoma volume) was also measured at each time-point, as previously described.16

**Baseline Patient Characteristics**

Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>&lt;150 mm Hg (n=34)</th>
<th>&lt;180 mm Hg (n=33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean±SD</td>
<td>71±12.6</td>
<td>68±11.3</td>
<td>0.29</td>
</tr>
<tr>
<td>Men</td>
<td>23 (68%)</td>
<td>26 (79%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Symptom onset to randomization, h</td>
<td>7.6 (13.7)</td>
<td>6.5 (11.3)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (74%)</td>
<td>25 (76%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>4 (12%)</td>
<td>1 (3%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Male</td>
<td>16 (47%)</td>
<td>16 (48%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Antihypertensive use</td>
<td>16 (47%)</td>
<td>15 (45%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Medication history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive use</td>
<td>16 (47%)</td>
<td>15 (45%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Antplatelet use</td>
<td>4 (12%)</td>
<td>0</td>
<td>0.11</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>0</td>
<td>4 (12%)</td>
<td>0.053</td>
</tr>
<tr>
<td>Baseline characteristics, mean±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>180.7±17.8</td>
<td>184.9±24.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>92.5±16.8</td>
<td>97.6±20.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>119±19.2</td>
<td>127±19.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76.8±14.7</td>
<td>79.7±17.7</td>
<td>0.47</td>
</tr>
<tr>
<td>NIHSS score, median (IQR)</td>
<td>10 (9)</td>
<td>12 (11.0)</td>
<td>0.89</td>
</tr>
<tr>
<td>GCS, median (IQR)</td>
<td>15 (3)</td>
<td>15 (2)</td>
<td>0.98</td>
</tr>
<tr>
<td>Hematoma location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>18 (53%)</td>
<td>12 (36%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Thalamus</td>
<td>8 (24%)</td>
<td>12 (36%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Lobar</td>
<td>7 (21%)</td>
<td>7 (21%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0</td>
<td>1 (3%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Hematoma volume, mL</td>
<td>14.1 (22.2)</td>
<td>17.2 (23.5)</td>
<td>0.41</td>
</tr>
<tr>
<td>Intraventricular volume, mL</td>
<td>0.0 (0.7)</td>
<td>0.0 (4.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>10 (29%)</td>
<td>15 (45%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Total ICH volume, mL</td>
<td>15.1 (20.9)</td>
<td>19.1 (31.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Edema volume (5–23 HU), mL</td>
<td>0.16±0.12</td>
<td>0.15±0.13</td>
<td>0.66</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IQR, interquartile range; NCCT, noncontrast computed tomography; and NIHSS, National Institutes of Health Stroke Scale.
Statistical Analysis
Baseline patient characteristics and effects of BP treatment were compared using independent t tests or Mann–Whitney tests. Paired sample t tests were used to compare perfusion measures within treatment groups. Pearson χ² or Fisher exact tests were used to compare frequencies of categorical data. The BP between treatment groups was considered statistically different when the 95% confidence intervals (CIs) of the means for each time-point did not overlap. Linear regression was used to assess for predictors of perihematoma edema growth. Intraclass correlation coefficients were calculated to assess inter-rater reliability for edema volume measurements, and Bland–Altman plots were used to illustrate the 95% limits of agreement for manual and 5 to 23 HU edema volume measurements.

Results
Patient Characteristics
A total of 75 patients were randomized in ICH ADAPT. One additional patient was randomized as part of a substudy19 and included in this analysis. Nine patients were excluded because of lack of a 24-hour NCCT (n=5), lack of CTP data (n=2), surgery (n=1), or death (n=1), leaving 67 patients in the final analysis. Treatment groups were balanced with respect to baseline clinical characteristics (Table 1).

BP Load and Weighted Average
BP reduction to each treatment target was achieved 1 hour after randomization (148±18 for the <150 group versus 165±16 for the <180 group; P<0.0001; Figure 2A). SBP in the <150 treatment group was lower than that in the <180 group at the 2-hour CTP scan (Table 2). High BP load (time spent, >180 mmHg) was lower in the <150 treatment group, indicating maintenance of BP control for the entire 24-hour postrandomization period. Weighted average SBP at 24 hours was also lower in the <150 treatment group (Figure 2B).

1-cm Region Cerebral Perfusion
Absolute CBF in the hemispheric and 1-cm ROIs was similar between BP treatment groups (Table 2). BP treatment did not affect mean rCBF in the 1-cm region (Table 2). Ipsilateral hemispheric rCBF was lower in patients randomized to the <150 group, relative to the <180 group (0.95±0.05 versus 0.99±0.05; P=0.002).

Edematous Region Cerebral Perfusion
Absolute CBF was lower in the edematous region (35.67±13.1 mL/100 g per minute) when compared with the contralateral 1-cm ROI (43.7±11.7 mL/100 g per minute; P<0.0001) and ipsilateral 1-cm ROI (38.18±12.4 mL/100 g per minute; P<0.0001). rCBF in the edematous region was similar between BP treatment groups (0.79±0.156 for <150 group versus 0.82±0.14; P=0.426). Absolute CBV was also lower in the edematous region (3.23±0.89 mL/100 g), relative to CBV in either the 1-cm (3.62±0.70 mL/100 g).

Figure 2. Blood pressure data and predictors of perihematoma edema growth. A, Blood pressure control >24 hours. Mean systolic blood pressure (SBP) differences at each time-point were considered significant (*) if the 95% confidence intervals did not overlap. B, Bar chart of mean weighted SBP, diastolic BP (DBP), and mean arterial pressure (MAP). C, Linear Regression (and 95% confidence intervals) for edema growth vs relative cerebral blood flow (rCBF) in the 1-cm perihematoma region. D, Regression for edema growth vs change in SBP, 0–2 h (mmHg).
Table 2. Blood Pressure Treatment Effects

<table>
<thead>
<tr>
<th>Variable</th>
<th>≤150 mm Hg</th>
<th>&gt;180 mm Hg</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute CBF measures, mL/100 g per minute (mean±SD)</td>
<td>37.8±13.6</td>
<td>38.7±11.0</td>
<td>0.76</td>
</tr>
<tr>
<td>Perihematoma</td>
<td>44.0±13.1</td>
<td>43.6±10.0</td>
<td>0.88</td>
</tr>
<tr>
<td>Ipsilateral hemispheric</td>
<td>41.2±12.6</td>
<td>42.2±8.77</td>
<td>0.73</td>
</tr>
<tr>
<td>Contralateral hemispheric</td>
<td>43.05±12.97</td>
<td>42.57±8.53</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Perihematoma Edema Volumes

Intraclass correlation coefficients for baseline perihematoma edema volume assessments were 0.95 (95% CI, 0.91–0.97) for manual edema assessment versus 0.92 (0.86–0.95; P=0.0001) for 5 to 23 HU. Coefficients at 2 hours were 0.967 (0.95–0.98; P<0.0001) and 0.977 (0.96–0.99; P<0.0001) and at 24 hours were 0.958 (0.93–0.97) and 0.99 (0.98–0.99; P<0.0001) for manual and HU measurements, respectively. Manually measured edema volumes were larger than those calculated using the HU threshold technique (Figure 3). The 95% limits of agreement were reduced when using 5 to 23 HU thresholds to measure edema volume (Figure 4). All subsequent comparisons involving edema used relative edema volumes calculated with the application of the 5 to 23 HU threshold.

Relative mean perihematoma edema volumes increased significantly from baseline (0.15±0.19) to 24 hours (0.25±0.20; P<0.0001) in all patients. The 2 BP treatment groups had similar edema volumes at 2 and 24 hours (Table 2). There was no difference in relative edema growth from 0 to 24 hours between the <150 and >180 BP groups (Table 2).

Predictors of Relative Edema Growth

Linear regression indicated that rCBF in the 1-cm region did not predict relative edema growth from 0 to 24 hours (β=–0.144; 95% CI, –0.647 to 0.167; P=0.244; Figure 2C). The rCBF in the edematous region was also unrelated to edema growth (β=–0.083; 95% CI, –0.371 to 0.186; P=0.508). The reduction in ipsilateral hemispheric rCBF was not associated with perihematoma edema growth (β=0.005; 95% CI, –0.845 to 0.880; P=0.968).

Edema growth was unrelated to the relative CBV in the edematous region (β=0.090; 95% CI, –0.059 to 0.127; P=0.470). Neither perihematoma relative mean transit time (β=–0.022; 95% CI, –0.056 to 0.047; P=0.863) nor relative CBV (β=0.018; 95% CI, –0.287 to 0.332; P=0.884) were related to relative edema growth. There was no interaction between edema growth and SBP change from randomization to 2 hours (β=–0.022; 95% CI, –0.002 to 0.001; P=0.858; Figure 2D).

Relative edema growth from 0 to 24 hours was not related to low BP load (β=0.091; 95% CI, –0.001 to 0.002; P=0.462) or high BP load (β=0.053; 95% CI, –0.004 to 0.006; P=0.569). Time from symptom onset to randomization (β=0.094; 95% CI, –0.004 to 0.008; P=0.449) and time from symptom onset to acute NCCT (β=–0.214; 95% CI, –0.021 to 0.001; P=0.829) were related to relative edema growth. Edema growth was not predicted by hematoma expansion >24 hours (β=–0.035; 95% CI, –0.004 to 0.003; P=0.778) or by acute hematoma volume (β=0.140; 95% CI, –0.003 to 0.001; P=0.260).

Discussion

We have shown for the first time that CBF in visibly edematous tissue is reduced. In this study, we found no relationship between perihematoma edema growth or BP treatment and CBF. Nonetheless, this is a relatively small study, and it remains possible that BP treatment may be related to perihematoma edema growth in some patients. The BP difference between our treatment groups was significant (21.3 mm Hg), but it is possible that even lower pressures may have an effect on perihematoma CBF and edema growth.
Defining Perihematoma Edema Volume
The border between hypodense edematous tissue and adjacent white matter is often difficult to define on CT scans. Most investigations rely on manual assessments, although statistical algorithms, including K-means clustering, have been used. We used HU thresholds, as previously described. Decreased x-ray attenuation in low-density edematous tissue is represented as a lower HU number. Our upper threshold (23 HU) reflected the mean of a range of HU that correlated with histologically confirmed edema. A lower threshold (5 HU) was used to exclude voxels containing cerebrospinal fluid spaces.

The Bland–Altman plots confirmed that HU threshold-assisted measurements improved consistency between raters (Figure 4).

1-cm Perihematoma Region Blood Flow
We demonstrated for the first time that hypoperfusion in a 1-cm perihematoma region is unrelated to edema growth >24 hours. Several studies have documented hypoperfusion in the perihematoma region, but few correlate this with edema volume, and none have assessed edema expansion. In an MRI perfusion study of 10 patients with acute ICH, edema volumes in patients with severe perihematoma hypoperfusion (defined...
as $T_{\text{max}}$ delay, >6s) were similar in patients with a delay of <6s.\(^7\) Another MRI perfusion study indicated that hypoperfusion was not an independent predictor of edema volume.\(^3\)

**Edematous Region Blood Flow**

We found that CBF was lower in visibly edematous tissue, relative to the 1-cm region surrounding the hematoma. This is consistent with the hypothesis that hypoperfusion is secondary to reduced metabolic demand.\(^22\) Whether this decreased flow is a cause of or secondary to edema cannot be determined from our data.

**Hematoma Volume and Edema Growth**

We found that hematoma volume and expansion were unrelated to perihematoma edema growth >24 hours. The dependence of edema volume on hematoma size is well established\(^25,26\) and is the rationale for using relative edema as the outcome variable when assessing for predictors of expansion.\(^18\) The lack of relationship between these variables in our study is likely because of small sample size.

**BP Control and Edema**

Acute BP reduction was not related to edema growth >24 hours, consistent with previous investigations of BP reduction and edema in ICH.\(^20,22\) In the Intensive BP Reduction in Acute Cerebral Hemorrhage Trial, patients with acute ICH were randomized to SBP targets of <140 and <180 mmHg.\(^20\) In 270 patients included in a secondary edema analysis, edema growth >72 hours was similar between treatment groups.\(^20\)

**Implications for Therapy**

Our results indicate that acute BP reduction does not lower CBF within 1-cm of the hematoma or in visibly edematous tissue or does it exacerbate edema volume expansion. These findings add support to the safety of acute BP lowering although we find no evidence that acute BP reduction attenuates edema expansion. This may reflect the fact that edema seems to be derived from plasma found in the hematoma itself and not additional fluid entering the brain from the vasculature.\(^27\) Thus, edema expansion may not represent the ideal treatment target for acute BP reduction.

**Limitations**

This study is limited by a lack of serial perfusion data. Perfusion imaging was completed at a single time-point (2 hours after randomization); thus, it is possible that subsequent blood flow changes affected perihematoma edema growth at 24 hours. However, clinical and experimental data suggest that perfusion deficits are most severe within the first 12- to 24-hour period\(^28\) and normalize subacutely.\(^23\) We assessed perihematoma edema volume (and growth) at only 1 relatively early time-point, which may not be as predictive of clinical outcome as that measured at later time-points. Ideally, a serial study of edema volume during the first week after symptom onset should be completed, to describe the relationship between all clinical variables and edema growth definitively. Finally, because of limitations in CTP coverage, CBF assessment did not encompass the entire perihematoma and visibly edematous regions in all patients, which may have affected the regression analyses. The magnitude of BP difference between groups although clinically significant, is modest, which is not unique to our trial.\(^20\) Importantly, the largest decrease and intergroup separation in BP was at 2 hours after randomization, when we assessed CBF.

This study is not powered adequately to determine all predictors of perihematoma edema growth because the biggest predictor of perihematoma volume is hematoma volume. Given the heterogeneity of sample size, a study of edema should involve several hundred patients at a minimum. As a CBF study of this size is not feasible, our aim was to assess the relationship between CBF and edema, which has been accomplished.

**Conclusions**

Acute BP reduction and lower CBF in the 1-cm perihematoma and visibly edematous regions do not affect edema growth >24 hours. Edema growth is predicted by hematoma expansion >24 hours. Our findings do not support a cytotoxic/ischemic pathogenesis of perihematoma edema.

**Sources of Funding**

The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH ADAPT) was funded by grant-in-aid support from Alberta Innovates Health Solutions (G513000128) and the Heart and Stroke Foundation of Canada (G220170180). Dr. Butcher holds a Canada Research Chair in Cerebrovascular Disease, a Heart and Stroke Foundation of Alberta Professorship in Stroke Medicine and a New Investigator Award from Alberta Innovates Health Solutions. Drs. Demchuk, Dowlatshahi, and Hill hold Heart and Stroke Foundation of Canada personnel awards. S.B. Coutts holds an Alberta Innovates Health Solutions New Investigator award. B. Gould and R. McCourt were supported by Alberta Innovates Health Solutions studentships.

**Disclosures**

None.

**References**


Cerebral Perfusion and Blood Pressure Do Not Affect Perihematoma Edema Growth in Acute Intracerebral Hemorrhage

Rebecca McCourt, Bronwen Gould, Laura Gioia, Mahesh Kate, Shelagh B. Coutts, Dariush Dowlatshahi, Negar Asdaghi, Thomas Jeerakathil, Michael D. Hill, Andrew M. Demchuk, Brian Buck, Derek Emery and Kenneth Butcher on behalf of the ICH ADAPT Investigators

Stroke. published online April 1, 2014;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://stroke.ahajournals.org/content/early/2014/04/01/STROKEAHA.113.003194

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/