Lack of Evidence for an Association Between Hemodynamic Variables and Hematoma Growth in Spontaneous Intracerebral Hemorrhage

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Background and Purpose—Early hematoma expansion in spontaneous intracerebral hemorrhage (ICH) is associated with worse clinical outcome. We hypothesized that hemodynamic parameters are associated with the increase in hematoma volume owing to their relationship to blood vessel wall stresses.

Methods—We performed a post hoc analysis of clinical and computed tomography (CT) data from patients enrolled in a prospective observational study of ICH patients presenting within 3 hours from symptom onset. Hematoma volumes were measured at hospital arrival and at 1 and 20 hours from presentation. Blood pressure and heart rate, recorded at 19 time points between presentation and 20 hours, were used to derive hemodynamic variables. Multivariable logistic-regression models were constructed to assess the relation between hemodynamic parameters and hematoma growth, adjusted for clinical covariates.

Results—From the original study, 98 patients underwent baseline and 1-hour CT scans; of these, 65 had 20-hour CT scans. Substantial hematoma growth was observed in 28% within the first hour. Of the 65 patients not undergoing surgery within 20 hours, 37% experienced hematoma growth by 20 hours. Neither baseline or peak hemodynamic parameters nor changes in hemodynamic parameters were significantly associated with hematoma growth at either 1 or 20 hours.

Conclusions—We found no blood pressure or heart rate parameters, individually or in combination, that were associated with hematoma growth. Our data suggest the influence of hemodynamic parameters on vessel wall stress to be an unlikely target for intervention in reducing the risk of early hematoma growth in ICH. (Stroke. 2006;37:2061-2065.)

Key Words: blood pressure ■ computed tomography ■ intracerebral hemorrhage
blood pressure and hematoma growth, hematoma growth is associated with poor outcome; thus, a relationship may exist between blood pressure, pulse pressure, and HR, or combinations of these parameters, and hematoma growth.\textsuperscript{2,4,6,21} The goal of this study was to investigate potential associations between hemodynamic variables and hematoma growth in spontaneous ICH. We hypothesized that hemodynamic parameters related to increasing stresses on the vessel walls are associated with hematoma growth.

**Patients and Methods**

**Study Design**

This study was a post hoc analysis of the clinical and computed tomography (CT) scan data of patients enrolled in a prospective observational study of spontaneous ICH.\textsuperscript{3} Patients with acute ICH were evaluated and enrolled by physicians with the Greater Cincinnati–Northern Kentucky Stroke Team. Inclusion criteria were age >18 years, evidence of ICH on head CT scan performed within 3 hours of symptom onset, and informed consent. Exclusion criteria were onset of symptoms >3 hours from presentation or unknown onset time (awoke with symptoms); hemorrhage due to trauma, tumor, ruptured arteriovenous malformation or aneurysm; or use of anticoagulants. Patients with subarachnoid hemorrhage (SAH) could be included if the study neuroradiologist determined that SAH was secondary to the ICH. Patients with isolated intraventricular hemorrhages were excluded.

On presentation to the emergency department, patients underwent a baseline noncontrast head CT scan per hospital protocol. After ICH was confirmed, the Stroke Team was notified, inclusion and exclusion criteria were reviewed, and informed consent was obtained.

Baseline demographics, past medical history, and current medications were recorded. Level of consciousness, HR, SBP, and DBP were recorded at presentation, every 30 minutes for 2 hours, every hour up to 12 hours, and then every 2 hours up to 24 hours. For each measurement, MAP (MAP = 1/3SBP + 2/3DBP) and pulse pressure (pulse pressure = SBP – DBP) were calculated. Because pressure parameters may combine with HR to play a role in the initiation and propagation of ICH by changing wall stresses, hemodynamic variables were created from combinations of HR and blood pressure: pulse pressure × HR to represent the pulse wave and (pulse pressure/ MAP) × HR to represent a pulse wave that is pressure adjusted.\textsuperscript{14}

Patients underwent repeat CT scans and neuroangiographic studies 1 and 20 hours from the baseline evaluation. CT scans were performed by scanners with a 512×512 matrix and 8- to 10-mm cuts. A single neuroradiologist identified all ICHs, SAHs, and intraventricular hemorrhages on the CT scans. All films were photographed, digitized, and analyzed according to established guidelines.\textsuperscript{1} Hematoma volume growth was defined as a one-third increase or more in volumes of ICH from baseline to minimize measurement artifact due to head positioning on CT slices between the initial and subsequent scans.

**Data Analysis**

Data are expressed as means and SDs. Comparison of clinical and hemodynamic parameters between groups used \( \chi^2 \) and unpaired \( t \) tests as appropriate. All statistical tests were 2 tailed, and statistical significance was predefined as \( P < 0.05 \).

For assessing the relation between hemodynamic parameters and hematoma growth, adjusted for clinical correlates, multivariable logistic regression was used. The means of the hemodynamic parameter values across the 1-hour or the 20-hour time periods and the peak values across the 1-hour or 20-hour time periods were considered primary independent variables. Models were adjusted for history of hypertension, aspirin use, and at 20 hours only, antihypertensive medica-
tion use. Other variables considered were time from symptom onset to first CT, current smoking, alcohol use, diabetes, and hematoma location. However, these were not entered into the regression models because none were statistically significant at \( P < 0.25 \) bivariately, and the sample size dictated caution regarding the number of independent variables in the model. Separate models were constructed for each hemodynamic parameter.

**Results**

Of the 142 patients from 12 hospitals within the stroke network initially screened for enrollment and who met inclusion criteria, 98 patients provided informed consent and had all required data elements for analysis. Overall, 74 patients (75.5%) were treated with antihypertensive medications during the first 20 hours. At 20 hours, 24 patients had undergone surgery: 10 patients had the clot removed, 3 had the clot removed and an intravenous catheter (IVC) placed, and 11 had an IVC placed only. One patient who had an IVC placed did not have hematoma volumes measured at 20 hours, and 9 patients who did not undergo surgery did not have hematoma volumes measured at 20 hours. Only 65 patients were analyzed at the 20-hour time point. The mean time from symptom onset to baseline CT scan for all 98 patients was 89 (SD, 37) minutes.

Hematoma growth was found in 28% (27/98) of patients within the first hour from presentation and in 37% (24/65) within the first 20 hours from presentation. Baseline demographic or clinical factors were not significantly different between those with and without hematoma growth (Table 1). The mean and peak hemodynamic parameters are shown in Table 2 for patients with and without hematoma growth. No hemodynamic parameter was associated with hematoma growth by multivariable logistic-regression analysis (Table 3).

The impact of hemodynamic parameters on hematoma growth at 20 hours was additionally assessed for patients not undergoing surgery combined with those who had an IVC placed. The results showed no impact of hemodynamic parameters on hematoma growth. Similarly, we considered the impact of hemodynamic parameters on hematoma growth at both 1 and 20 hours and excluded those patients with a posterior fossa ICH. Similarly, no hemodynamic parameters predicted hematoma growth (results not shown).

**Discussion**

Several previous publications have described factors associated with hematoma enlargement in primary ICH, including previous brain infarct, liver disease, excessive alcohol consumption, regular aspirin use, hyperglycemia, admission SBP, maximum SBP, and fibrinogen levels.\(^4,6,11,21\) Several reports on the association between blood pressure and morbidity/mortality

### TABLE 2. Hemodynamic Parameters for the 0–1-Hour and 0–20-Hour Time Periods

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1-Hour Growth</th>
<th>20-Hour Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP, mm Hg</strong></td>
<td>Total n=98</td>
<td>Growth n=27</td>
</tr>
<tr>
<td>Peak</td>
<td>191 (31)</td>
<td>191 (26)</td>
</tr>
<tr>
<td>Mean</td>
<td>175 (28)</td>
<td>180 (25)</td>
</tr>
<tr>
<td><strong>DBP, mm Hg</strong></td>
<td>Peak</td>
<td>110 (23)</td>
</tr>
<tr>
<td>Mean</td>
<td>100 (20)</td>
<td>102 (18)</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>Peak</td>
<td>88 (23)</td>
</tr>
<tr>
<td>Mean</td>
<td>75 (19)</td>
<td>78 (18)</td>
</tr>
<tr>
<td><strong>MAP, mm Hg</strong></td>
<td>Peak</td>
<td>135 (24)</td>
</tr>
<tr>
<td>Mean</td>
<td>126 (20)</td>
<td>128 (19)</td>
</tr>
<tr>
<td>HR, beats per min</td>
<td>Peak</td>
<td>88 (19)</td>
</tr>
<tr>
<td>Mean</td>
<td>82 (170)</td>
<td>82 (14)</td>
</tr>
<tr>
<td>Pulse pressure×HR, mm Hg/min</td>
<td>Peak</td>
<td>7234 (2396)</td>
</tr>
<tr>
<td>Mean</td>
<td>6208 (2066)</td>
<td>6463 (1465)</td>
</tr>
<tr>
<td>MAP×HR, mm Hg/min</td>
<td>Peak</td>
<td>11 534 (2843)</td>
</tr>
<tr>
<td>Mean</td>
<td>10 288 (2777)</td>
<td>10 352 (2493)</td>
</tr>
<tr>
<td>(Pulse pressure×HR)/MAP, min(^{-1})</td>
<td>Peak</td>
<td>58 (17)</td>
</tr>
<tr>
<td>Mean</td>
<td>50 (16)</td>
<td>51 (9)</td>
</tr>
</tbody>
</table>

Mean and standard deviation of the mean (average value over 1 or 20 hours) and peak (maximum value over 1 or 20 hours) of the parameter values are shown. There were no differences between patients with growth of hematoma and patients without growth, either at 1 or 20 hours.
in ICH suggest worse outcomes at either extreme of blood pressure values.  

Identifying a relation between blood pressure or other hemodynamic parameters and hematoma growth would suggest an immediate target for intervention to possibly improve outcomes in patients with spontaneous ICH and might settle the controversy surrounding the optimal management of blood pressure in the ICH patient.

This post hoc analysis of data from Brott and colleagues attempted to identify hemodynamic variables potentially associated with hematoma growth. No associations between baseline, peak, and mean hemodynamic parameters and hematoma growth were found. The lack of association between blood pressure and hematoma expansion is in contrast to some previously published reports. Fujii et al reported an association between high admission SBP and hematoma growth in their series of 419 patients with spontaneous ICH. Ohwaki et al reported that peak SBP after hospital admission was associated with hematoma enlargement but also found that admission SBP and time from onset were not associated with hematoma enlargement. However, onset time was unknown for 18 of 76 patients included in this series, and patients on anticoagulants were included in the analysis, unlike those in other reports. Kazui et al found a high risk of hematoma enlargement in poorly controlled diabetics with a high SBP (≥200 mm Hg) on admission.

To our knowledge, these reports represent the state of the art with regard to understanding the effects of hemodynamic parameters on hematoma enlargement in ICH. None used prospectively collected data in the hyperacute period of ICH, when most hemorrhage growth is reported to occur. Similarly, none examined parameters beyond SBP and DBP nor provided detailed information on the time of elevated blood pressure measurement and the incidence of hematoma growth. Our study of ICH patients presenting within 3 hours of symptom onset with a repeat CT scan obtained at 1 and 20 hours after the baseline CT scan showed no association between hemodynamic parameters and hematoma growth.

Although our study represents a significant advance over prior work, several limitations remain. Transient blood pressure and HR elevations often occur secondary to noxious stimuli (intubation, IVC placement, Foley catheterization), and despite numerous blood pressure measurements taken in this study, transient elevations may not have been captured. Similarly, elevations in blood pressure during the first 20 hours may represent a response to increasing intracranial pressure (Cush-
ing’s reflex) and may not be causal in hemorrhage growth. Using baseline hemodynamic variables would likely minimize the confounding effect of increasing intracranial pressure. Given the pathophysiological differences between the development of lobar and nonlobar hemorrhages, the relatively small number of patients prevents the identification of significant differences in blood pressure and hematoma growth as a function of location. Other studies have found associations between fibrinogen/cellular fibronectin levels and hematoma enlargement; unfortunately, in the original study, those levels were not assessed. 2,18 There is some evidence of selection bias for our analysis of 20-hour hematoma volume growth; baseline and 1-hour hematoma volumes were larger in those patients lost to 20-hour follow-up than in those remaining in the analysis, reflecting more severely affected patients who died in the 20-hour interval, were too moribund for repeat CT, or required emergent surgery and/or IVC placement. Generalizability across the entire spectrum of disease severity may be limited. Lastly, as noted in the original article, 76% of patients received antihypertensive medication, potentially obscuring “any relationship between sustained elevated blood pressure and hemorrhage growth.”

Conclusion
Our data do not support our hypothesis that hemodynamic parameters are likely therapeutic targets to limit early hematoma growth in ICH. The pathophysiological role of elevated blood pressure in hematoma growth after ICH remains unclear. Larger prospective studies, such as that proposed by Qureshi et al., 29 are warranted to define the optimal blood pressure goals in ICH patients and to identify other factors suitable for intervention to minimize hematoma growth and subsequent clinical deterioration.

Acknowledgments
The authors thank Rashmi Kothari, MD, Thomas Tomswick, MD, Laura Sauerbeck, RN, Judith Spilker, RN, John Duldner, MD, and Rosie Miller, RN, for their efforts on the original project.

Source of Funding
This study was supported in part by the National Institute of Neurological Disorders and Stroke Grant NS26933.

Disclosures
None.

References
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StROKE. 2006;37:2061-2065; originally published online June 22, 2006;
doi: 10.1161/01.STR.0000229878.93759.a2
StROKE is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/37/8/2061

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