Effects of Hypobaric Hypoxia on Cerebral Autoregulation

Andrew W. Subudhi, PhD; Ronney B. Panerai, PhD; Robert C. Roach, PhD

Background and Purpose—Acute hypoxia is associated with impairment of cerebral autoregulation (CA), but it is unclear if altered CA during prolonged hypoxia is pivotal to the development of cerebral pathology, such as that seen in acute mountain sickness (AMS). This investigation evaluated relationship between CA and AMS over 9 hours of hypobaric hypoxia.

Methods—Fifty-five subjects (41 males, 14 females) were studied in normoxia (P_B = 625 mm Hg) and after 4 and 9 hours of hypobaric hypoxia (P_B = 425 mm Hg; ≈ 4875 m). Resting, beat-by-beat changes in arterial blood pressure, and middle cerebral artery blood flow velocity were recorded at each time point while breathing room air. Transfer function analyses were used to estimate autoregulation indices (ARI). In 29 subjects, ARI during isocapnic hyperoxia and cerebral vasomotor reactivity during modified rebreathing were also determined to isolate effects of hypoxia and CO_2 reactivity on CA.

Results—Self-reported Lake Louise AMS Questionnaire scores ≥ 3 with headache were used to differentiate between AMS-positive (n = 27) and AMS-negative (n = 28) subjects (P < 0.01). ARI decreased and CO_2 reactivity increased in both groups at 4 hours (P < 0.01) and did not progress at 9 hours, despite increased incidence and severity of AMS (P < 0.01). Impairments in ARI were alleviated with isocapnic hyperoxia at 4 and 9 hours (P < 0.01) and were not related to CO_2 reactivity.

Conclusions—These results indicate that hypoxia directly impairs CA but that impaired CA does not play a pivotal role in the development of AMS. (Stroke. 2010;41:641-646.)

Key Words: acute mountain sickness ■ altitude ■ cerebral blood flow ■ transcranial Doppler ■ vascular reactivity

In healthy individuals, cerebral autoregulation (CA) effectively buffers changes in perfusion pressure to maintain consistent blood flow. CA is impaired in diseases in which hypoxia occurs secondary to ischemia (eg, stroke), carotid artery stenosis, and traumatic brain injury; however, whether hypoxic impairment of CA contributes to the progression of such diseases has not been established. Whereas we and others have recently shown that acute hypoxia (≈ 10 minutes) impairs CA, it is unknown if such impairment persists during prolonged periods of hypoxia (eg, hours) and leads to the development of cerebral pathology. Acute mountain sickness (AMS) offers a unique clinical model to address this question because the illness can be induced and reversed in controlled laboratory settings.

It has been hypothesized that elevated cerebral blood flow and impaired CA during acute hypoxia may disrupt the blood–brain barrier, causing vasogenic edema. Ensuing meningeal stress or increased intracranial pressure, if cerebral compliance is limited, could be responsible for headache, dizziness, and nausea that define AMS. This hypothesis appears to be supported by a few studies showing that CA is impaired after AMS has developed (6–48 hours) and that the degree of CA impairment is moderately correlated with AMS symptomology (r^2 = 0.20–0.50); however, no studies have reported serial measurements of CA as AMS develops to establish a definitive link between impairment of CA and onset of AMS. Additionally, because CA remains impaired after successful acclimatization to high altitude and persists in life-long residents of high altitude, a relationship between CA and AMS remains questionable. We report the first (to our knowledge) sequential measurements of CA during 9 hours of hypobaric hypoxia to test the hypothesis that changes in CA would be directly related to the development of AMS.

Materials and Methods

Recruitment and Screening

After institutional ethics approval, potential subjects were screened to identify those with no histories of head injuries, migraines, smoking, or medical conditions affected by hypoxia, such as anemia, pregnancy, or hypertension. Additionally, a brief altitude history was obtained to exclude those with recent (< 1 month) exposure to altitudes > 2500 m. After obtaining written consent, volunteers were physically examined and excluded if results revealed previously undisclosed medical conditions, or if they were not able to achieve at
least 200 W of effort during an incremental cycle ergometer test. Of 66 consenting subjects, 55 (41 males, 14 females) meeting the inclusion criteria completed the following protocol.

Protocol
This study represents the placebo arm of a large, multiyear study investigating cerebral pathophysiology resulting from hypoxia. All subjects received placebo medications 24 hours before baseline (BL) measurements ($P_{Hb}$, 625–630 mm Hg; relative humidity, 12%–28%; 19°C–23°C) and throughout a 10-hour period in a hypobaric chamber ($P_{Hb}$, 425 mm Hg; relative humidity, 13%–29%; 19°C–22°C) the next day. Inside the chamber, subjects performed 4 30-minute sets of submaximal cycling (50% altitude specific VO$_2$max), with 15 minutes of rest between sets, to increase the incidence of AMS. Subjects then rested for the remaining 7 hours of hypoxia. Measures of CA and AMS were evaluated at BL, 4 hours, and 9 hours, as described.

In one cohort, 26 subjects (16 males, 10 females) rested in a supine position for 15 minutes while being instrumented to monitor beat-by-beat changes in arterial blood pressure (ABP) via a tonometer placed over the right radial artery (Colin 7000; Colin Medical Instruments) and middle cerebral artery blood flow velocity (CBFv) insomed via the ipsilateral temporal window at depths of ~50 mm (Model Multi Dop T2; DWL Electronic Systems). Doppler probes were secured to a custom headset to preserve insonation angle and traced with indelible ink to guide subsequent replacements. Data were then recorded for 6 to 10 minutes for transfer function analysis of CA while breathing room air ($P_{O2}$, 0.21) to assess poikilocapnic responses to hypobaric hypoxia that would be expected in field conditions.

In a second cohort, 29 subjects (25 males, 4 females) were studied in a similar manner using a second set of blood pressure (Nexfin HD; Bmeye) and Doppler (Spencer Technologies) instruments. To isolate the effect of hypoxia on CA and control for potentially confounding effects of $Paco_2$, subjects in this cohort were also monitored to assess CA during 6 to 10 minutes of isocapnic hyperoxia at each time point using 49% $O_2$ (balance $N_2$) at BL and 79% $O_2$ under hypobaric conditions to maintain $P_{O2}$ at ~250 mm Hg. Isocapnia was achieved by manually adjusting the flow of hyperoxic gas using the sequential gas delivery system. Additionally, cerebral vasomotor reactivity to $CO_2$ (CVMR) during a modified rebreathing protocol (6-L reservoir filled with gas to produce a $P_{O2}$ of 250 and $P_{CO_2}$ of 50 mm Hg at each period) was evaluated to determine the relative influence of $CO_2$ reactivity on CA.

In all experiments, expired gases and volumes were analyzed using fast response analyzers (Ametek S-3A and CD-3A; AEI Technologies; or $O_2$cap; Oxigraph) and a heated pneumotach (Hans Rudolph). Blood oxygen saturation was monitored by finger-pulse oximetry (N-595; Nellcor) and ECG via standard 3-lead configuration (Bioamp; ADInstruments). Analog signals from each instrument were integrated with a data acquisition system (Powerlab 16SP; ADInstruments), which sampled at 200 Hz throughout the experimental periods.

Self-reported sections (headache, gastrointestinal distress, dizziness, fatigue) of the Lake Louise AMS Questionnaire were used to evaluate AMS symptoms at BL, 4 hours and 9 hours. Subjects with Lake Louise AMS Questionnaire score $\leq$3 with headache at 9 hours were defined as AMS-positive (AMS$^+$); those with Lake Louise AMS Questionnaire score $\leq$2 or without headache were defined as AMS-negative (AMS$^-$).

Table 1. Effects of Hypobaric Hypoxia in AMS$^-$ (n=28) and AMS$^+$ (n=27) Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>BL</th>
<th>4 Hours</th>
<th>9 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{O2}$</td>
<td>4.04±0.74</td>
<td>4.04±0.64</td>
<td>4.00±2.29*</td>
</tr>
<tr>
<td>$V_{E}$</td>
<td>9.58±2.12</td>
<td>8.89±1.76</td>
<td>10.46±4.25</td>
</tr>
<tr>
<td>Pet$O_2$, mm Hg</td>
<td>79.3±5.5</td>
<td>79.2±5.0</td>
<td>45.7±5.2</td>
</tr>
<tr>
<td>Pet$CO_2$, mm Hg</td>
<td>36.1±3.2</td>
<td>36.3±3.3</td>
<td>29.5±3.6</td>
</tr>
<tr>
<td>SpO$_2$, %</td>
<td>96.0±1.5</td>
<td>96.1±1.7</td>
<td>84.0±7.5</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>63.2±11.7</td>
<td>60.1±8.0</td>
<td>89.1±13.2</td>
</tr>
<tr>
<td>Mean $ABP$, mm Hg</td>
<td>91.5±13.9</td>
<td>86.6±10.8</td>
<td>79.9±9.6</td>
</tr>
<tr>
<td>Mean CBFv, cm/sec</td>
<td>58.6±8.9</td>
<td>57.1±12.5</td>
<td>57.3±11.7</td>
</tr>
<tr>
<td>CVRi, mm Hg/cm/sec</td>
<td>1.60±0.35</td>
<td>1.60±0.44</td>
<td>1.48±0.40</td>
</tr>
<tr>
<td>Transfer function analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABP PSD, mm Hg$^2$/Hz</td>
<td>9.41±4.44</td>
<td>7.01±4.97</td>
<td>9.19±6.50</td>
</tr>
<tr>
<td>CBFv PSD, cm$^2$/sec$^2$/Hz</td>
<td>7.85±5.15</td>
<td>7.55±6.27</td>
<td>18.14±14.22</td>
</tr>
<tr>
<td>Coherence</td>
<td>0.52±0.11</td>
<td>0.47±0.14</td>
<td>0.60±0.14</td>
</tr>
<tr>
<td>Gain, %/°</td>
<td>0.63±0.20</td>
<td>0.71±0.28</td>
<td>1.12±0.48</td>
</tr>
<tr>
<td>Phase, rad</td>
<td>0.54±0.31</td>
<td>0.55±0.35</td>
<td>0.35±0.21</td>
</tr>
<tr>
<td>Step response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR1</td>
<td>4.70±1.10</td>
<td>4.11±1.53</td>
<td>3.30±1.11</td>
</tr>
<tr>
<td>%CBFv recovery</td>
<td>66.8±13.7</td>
<td>57.6±25.0</td>
<td>42.4±17.9</td>
</tr>
</tbody>
</table>

Transfer function analysis results from low-frequency range (<0.10 Hz). Different from *AMS$^-$, †BL, and ‡4 hours at a $P$<0.01. CVRi indicates cerebrovascular resistance index; HR, heart rate; LLQ, Lake Louise AMS Questionnaire; PSD, power spectral density; SpO$_2$, blood oxygen saturation.

Analyses
CA was determined using transfer function analysis and subsequent step response, as previously described, to quantitatively describe the effects of spontaneous changes in blood pressure on cerebral blood flow velocity. Briefly, resting ABP and CBFv tracings were cleaned for removal of random signal noise and smoothed using median (5 points) and Butterworth filters in succession. Beat-by-beat data were extracted and resampled at 5 Hz. Fast-Fourier transformations using the Welch algorithm with 512-point windows and 40% overlap were performed to obtain power spectral densities of ABP and CBFv. The average power spectral densities, coherence, gain, and phase shift were evaluated in the low-frequency range of autoregulation (<0.10 Hz).
Hz), associated with cycle lengths >10 sec. An inverse fast-Fourier transformation was then performed using both gain and phase shift to yield an impulse response in the time domain. Integration of the impulse yielded a step response that was fit to one of Tiecks et al.’s autoregulation index models (ARI) and used to determine percent CBFv recovery 4 sec after the peak impulse,6 in which higher scores are reflective of better CA (ARI range, 0–9; percent recovery after peak impulse range, 0%–100%).

CVMR was defined as the slope of the linear fit between percent resting CBFv and PetCO2 during modified rebreathing.24 Additionally, the cerebrovascular conductance index, which corrected CVMR for changes in ABP, was calculated from the slope of the linear fit between percent resting CBFv/ABP and PetCO2.25

Statistics
Preliminary analyses indicated no differences between the 2 cohorts in cardiorespiratory, cerebrovascular, or transfer function analysis results, so data were pooled for further analysis. CA and CVMR measurements were analyzed using mixed factor ANOVA, with AMS status (AMS+ vs AMS−) analyzed over time (BL, 4 hours, and 9 hours) for room air and hyperoxic conditions. Criteria for significance were set at $P<0.05$ for main and interaction effects; $t$ tests were used for post hoc analyses of differences across time and $FIO2$ (paired) and between AMS status (independent) using more stringent criteria ($P<0.01$) to control for type I error. Pearson product moment correlations were calculated between CA, CO2 reactivity, and AMS scores at 4 and 9 hours ($P<0.05$). Data are presented as means±SD.

Results
Subjects completing the protocol were 29±7 years old, 178.2±9.9 cm tall, and weighed 74.4±12.5 kg. Hypoxia decreased blood oxygen saturation, PetO2, and PetCO2, and increased $V_e$ and heart rate at 4 and 9 hours ($P<0.05$). Mean ABP was lower at 4 hours compared to that at BL and 9 hours ($P<0.01$). None of these effects was different between AMS+ ($n=27$) and AMS− ($n=28$) subjects (Table 1). Composite Lake Louise AMS Questionnaire and headache severity scores increased from 4 to 9 hours in the AMS+ group only (Table 1). No individuals who met the criteria for AMS at 4 hours were AMS− at 9 hours.

Cerebral Autoregulation
Table 1 displays the results of the transfer function analysis and step responses while breathing room air ($FIO2$=0.21) at each time point. Fast-Fourier transformations of time series data from both cohorts revealed hypobaric hypoxia resulted in pronounced low-frequency oscillations (>10 sec/ cycle) in power spectral densities of CBFv ($P<0.01$), but not ABP. Transfer function analysis showed stronger relationships (coherence), greater transmittal of signal amplitudes (gain), and smaller phase shifts between ABP and CBFv, suggesting impairment of CA at 4 and 9 hours of hypoxia ($P<0.01$). These findings were confirmed by ARI (Figure 1) and percent recovery after peak impulse scores derived from the step response ($P<0.01$). No differences were detected between AMS− and AMS+ groups at any time point, even when groups were stratified by the highest (50%) vs lowest (50%) AMS scores or blood oxygen saturation values.13 Correlations between ARI and Lake Louise AMS Questionnaire scores (composite and headache subscale) were not significant at either 4 ($r=-0.13; P=0.37$; Figure 2) or 9 hours ($r=-0.05; P=0.72$; Figure 2).
Table 2. Effects of Isocapnic Hyperoxia (n=29)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Room Air</th>
<th>Hyperoxia</th>
<th>Room Air</th>
<th>Hyperoxia</th>
<th>Room Air</th>
<th>Hyperoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_e$, L/min</td>
<td>9.32±2.15</td>
<td>11.47±3.49*</td>
<td>12.32±4.08†</td>
<td>12.28±4.90</td>
<td>12.66±3.05†</td>
<td>12.79±4.63</td>
</tr>
<tr>
<td>Pet$O_2$, mm Hg</td>
<td>79.4±4.2</td>
<td>241.9±15.1*</td>
<td>44.4±3.4†</td>
<td>248.7±14.9*</td>
<td>44.4±4.8†</td>
<td>245.9±15.8*</td>
</tr>
<tr>
<td>Pet$CO_2$, mm Hg</td>
<td>35.9±2.8</td>
<td>35.2±2</td>
<td>30.0±3.0†</td>
<td>31.4±3.4†</td>
<td>30.8±3.1†</td>
<td>31.3±3.1†</td>
</tr>
<tr>
<td>$SpO_2$, %</td>
<td>95.4±1.1</td>
<td>98.8±0.4*</td>
<td>81.4±6.1†</td>
<td>98.9±0.28*</td>
<td>78.9±7.0†</td>
<td>98.9±0.3*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>62.4±8.9</td>
<td>61.0±9.1</td>
<td>89.7±11.7†</td>
<td>76.9±12.7†</td>
<td>94.8±13.0†</td>
<td>78.6±12.2†</td>
</tr>
<tr>
<td>Mean ABP, mm Hg</td>
<td>91.1±10.9</td>
<td>97.5±12.9*</td>
<td>79.6±12.3†</td>
<td>90.5±10.8*</td>
<td>87.3±11.7†</td>
<td>93.9±10.3*</td>
</tr>
<tr>
<td>Mean CBFv, cm/sec</td>
<td>54.4±7.2</td>
<td>54.9±8.9</td>
<td>52.8±8.9</td>
<td>48.2±9.2†</td>
<td>56.5±9.8</td>
<td>48.2±9.8†</td>
</tr>
<tr>
<td>CVRi, mm Hg/cm/sec</td>
<td>1.70±0.26</td>
<td>1.82±0.35</td>
<td>1.54±0.31</td>
<td>1.94±0.44*</td>
<td>1.59±0.31</td>
<td>2.04±0.53†</td>
</tr>
</tbody>
</table>

Transfer function analysis results from low-frequency range (<0.10 Hz). Different from *room air, †BL, and ‡4 hours at P<0.01.

Effect of Isocapnic Hyperoxia
The manual sequential gas delivery method enabled us to rapidly adjust Pet$O_2$ to ≈250 mm Hg while maintaining Pet$CO_2$ (Table 2). Isocapnic hyperoxia increased blood oxygen saturation, ABP, and cerebrovascular resistance (cerebrovascular resistance index = ABP/CBFv) at all time points (P<0.01) and decreased CBFv at 4 and 9 hours (P<0.01). Impairments in CA at 4 and 9 hours of hypoxia were completely alleviated during isocapnic hyperoxia (Figure 3), as indicated by reductions in coherence and gain coupled with increases in phase shift, ARI, and percent recovery after peak impulse (P<0.01).

Reactivity to Carbon Dioxide
CVMR increased continually over 9 hours of hypoxia, with AMS+ (n=11) showing greater reactivity than AMS− (n=18) at 9 hours (P<0.01) in the second cohort; however, when corrected for changes in blood pressure (ie, cerebrovascular conductance index), differences between groups were not significant (Table 3). Lake Louise AMS Questionnaire scores were moderately correlated with CVMR at 9 hours (r=0.55; P<0.01), but not with cerebrovascular conductance index (r=0.19; P=0.34).

Discussion
Results from this study refute the prevalent hypothesis that impairment of CA is a pivotal element in development of AMS. We tested the hypothesis that CA would become more impaired as AMS developed in subjects during 9 hours of hypobaric hypoxia; however, our data demonstrate evidence to the contrary. Whereas hypoxia did impair CA, changes were similar in those in whom AMS developed and in those who remained healthy. Additionally, we found no evidence to suggest that the degree of CA impairment was related to the progression of AMS over 9 hours of hypoxia. These results indicate that hypoxia directly impairs CA, but that impaired CA does not explain the development of AMS.

Our data differ from previous studies that have reported moderate associations between CA and AMS scores. Variations in methodology and interpretation may explain the different conclusions. First, in 2 of the aforementioned studies, correlations between transfer function analysis gain scores and AMS symptomology were used to suggest modest links between CA and AMS ($r^2\sim0.50$). We also found a small but significant correlation between gain and Lake Louise AMS Questionnaire scores; yet, as we have
previously argued, increased gain without a reduction in phase shift is insufficient to imply impaired CA. In the present study, we restricted our conclusions to composite ARI and percent recovery after peak impulse scores, which are based on a combination of gain and phase scores, to avoid reporting potentially spurious relationships. Second, studies using the leg-cuff technique to assess CA have also reported modest relationships with AMS; yet, results explained less than half of the variance seen in AMS scores and were only measured after the onset of AMS, making it difficult to draw conclusions regarding the role of impaired CA in the development of AMS.

Despite these differences, our results are in close agreement with the body of literature concerning CA during hypoxia. Previous studies have shown that hypoxia impairs CA within 10 minutes of exposure, long before symptoms of AMS are evident. Our serial measurements of CA now demonstrate that this effect is consistent at 4 and 9 hours, with no difference between those with AMS developing and those remaining healthy. Because similar impairment in CA has been demonstrated in healthy individuals after 1 to 2,5 to 7,15 9,14 and 30 days of acclimatization to hypoxia, as well as in lifelong residents in high altitudes (>,4200 m), we can safely assert that CA impairment is likely to be a natural response to hypobaric hypoxia. What remains to be determined is why. It is conceivable that during severe hypoxia, vasodilatory responses to maintain cerebral blood flow and oxygenation may override or counteract CA mechanisms that could effectively restrict blood flow (eg, reduced PacO2) in a time of need. Further studies are needed to elucidate the significance of apparently impaired CA in otherwise healthy individuals in chronic hypoxia.

To isolate the effects of hypoxia from hypocapnia, we expanded our experimental protocol to include supplementary measurements in our second cohort. Because PacO2 is known to alter CA26 and is affected by changes in ventilatory drive during hypoxia and hyperoxia, we held PetCO2 constant while increasing PacO2 to ≈250 mm Hg at each time point. At BL, CA was unaffected; however, at 4 and 9 hours impairments in CA were completely reversed by isocapnic hyperoxia (Figure 3). These results imply that low PacO2, rather than PaCO2 or hypobaria, was the predominant stimulus impairing CA. Additionally, potential contributions from changes in CO2 reactivity to the integrated CA response were evaluated using modified CO2 rebreathing at each time point. Results showed that blood pressure-corrected measures of CO2 reactivity increased progressively over 9 hours of hypoxia but were unrelated to poikilocapnic assessments of resting CA. These findings support our conclusion that hypoxia per se is the driving factor suppressing CA during hypobaric hypoxia.

In seeking to explain the mechanism by which hypoxia affects CA, our attention was drawn to patterns seen in mean CBFV tracings, in which slow, cyclic variations (<0.10 Hz; >10 sec/cycle) were visibly amplified during hypoxia and attenuated during hyperoxia. Because intact CA should effectively dampen changes in CBFV, the mechanisms allowing or generating these large oscillations during hypoxia are of particular interest. We speculate that hypoxia may be amplifying fluctuations in CBFV either by the augmented ABP to CBFV gain or by stimulation of rhythmic brain stem activity purported to control cerebral vessel tone and intracranial pressure.28–30 Such brain stem-derived effects may superead or mask mechanisms responsible for CA in normoxia and may explain why hypoxia amplified slow oscillations in CBFV in the brain, but not in ABP measured in the radial artery. This hypothesis could be tested by short-term blocking of specific neurotransmitter activity during acute hypoxic exposure, because hypoxic effects on CA can be detected within 10 minutes and readily reversed with supplemental oxygen. Thus, hypoxia offers a promising model for isolating mechanisms contributing to the integrated CA response and may lead to new methods of clinical treatment for those in whom impaired CA secondary to hypoxia increases the risk for cerebrovascular complications.

**Summary**

Hypoxia alone appears to directly impair CA; however, impaired CA does not explain the onset or development of AMS. Hypoxia offers a unique model for investigating the mechanisms responsible for impaired CA as assessed by transfer function analysis because it can be studied in controlled laboratory settings with minimal risk to subjects.

**Acknowledgments**

The authors express their gratitude to Alison Anderson, BS, Jason Chapman, PhD, Andrew Dimmen, MSc, Ruth Johnson, BS, Colleen Julian, MD, Travis Pecha, BS, Nicholas Robbins, BS, Paige Sheen, MS, and Megan Wilson, PhD, for all their efforts in study management and data collection. The authors also extend their appreciation to Vaughn Browne, MD, PhD, Holly Frankland, BS, RN, and Janet Uhde, MD, for their medical support throughout the study.

**Sources of Funding**

Funding was provided by National Heart, Lung, and Blood Institute grant HL-070362 and the Altitude Research Center.

**Disclosure**

None.
References


Effects of Hypobaric Hypoxia on Cerebral Autoregulation
Andrew W. Subudhi, Ronney B. Panerai and Robert C. Roach

*Stroke*. 2010;41:641-646; originally published online February 25, 2010;
doi: 10.1161/STRKEAHA.109.574749
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 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/41/4/641

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/